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ENDOTHELIAL MYELOMA, EWING*

REPORT OF FIFTY-FOUR CASES

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The following report is based on fifty-two cases of bone tumors classified as Ewing's tumor in the Registry of Bone Sarcoma of the American College of Surgeons,[1] and two cases selected as roentgenologic and histologic types from the Massachusetts General Hospital, Boston. The number of cases in the sarcoma registry so classified is sixty-seven, or about 10 per cent. of the total registered, but some do not contain sufficient data to make a definite diagnosis, or so closely resemble other tumors, particularly osteogenic sarcomas, that they could not be included. Cases, also, in which there is too great variation in opinion have been excluded, although, in my opinion, they may belong to this group.

It must be mentioned that the data received by the registry, which usually includes the clinical history, roentgenograms and sections for microscopic study, were sent around to various pathologists and surgeons for diagnosis. This tumor particularly has brought forth a divergence of opinion and nomenclature that shows the confusion concerning it that exists in the minds of the foremost men in these branches of medicine. It has been classified heretofore as round cell sarcoma of bone, and, though it has been recognized by many as of somewhat different nature from the usual osteogenic sarcoma or myeloma, Ewing[2] has been one of the few in this country to place it among the endotheliomas. It has therefore been given his name by the registrar, as many do not think its origin proved, and they hesitate to call it endothelioma until convinced that such, indeed, it is. In the following paper it will be called endothelial myeloma to distinguish it from other forms of myeloma; the reason for this will appear later.

It was with the idea of correlating the opinions held and making as careful a histologic investigation as possible that this work was begun. It has not been generally known that the clinical course is rather char-

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1. The Committee on Bone Sarcoma of the American College of Surgeons consists of Drs. James Ewing, J. C. Bloodgood and E. A. Codman, registrar.

2. Ewing, J.: Neoplastic Diseases, Ed. 2, Philadelphia, W. B. Saunders Company, 1922, pp. 322-328.

acteristic, and that the histology, though often confused with that of other myelomas, fibrosarcomas and metastatic tumors, is nevertheless distinctive. The tumors presented here have all been accepted by Ewing as endothelial myeloma or endothelioma, and most of them have been passed on by the following pathologists and surgeons: Drs. S. B. Wolbach, F. B. Mallory, J. H. Wright, H. F. Hartwell and L. W. Smith of Boston; Douglas Symmers, C. J. MacGuire, Jr., J. E. McWhorter, A. P. Stout, W. C. Clarke, F. C. Wood and F. C. Christensen of New York; J. B. McFarland, Herbert Fox, Balduin Lucké, J. R. Paul, E. A. Case, C. Y. White and John Speese, Philadelphia; J. C. Bloodgood and W. G. MacCallum, Baltimore; Allen Graham and E. C. Cutler, Cleveland; J. F. Coupal and G. R. Callender, Washington; L. Hektoen, D. B. Phemister, Kellog Speed and F. C. Zapffe, Chicago; S. R. Haythorne, Pittsburgh; E. T. Bell, Minneapolis; W. C. MacCarty, Rochester, Minn.; A. S. Warthin, Ann Arbor, Mich.; W. C. Duffy and J. J. Morton, New Haven, Conn.; K. M. Lynch, Dallas, Texas; W. L. Robinson, Toronto; V. H. Keiller, Galveston, Texas, and others. Not all these have accepted it as differing so greatly from other tumors arising in bone that it needs a separate classification, but Wolbach, Mallory, Bloodgood, Smith, Phemister, Coupal and others have felt that as to histology it is distinct. It is believed that by elimination nearly all tumors that might fall into any other group have been so classified, and the remainder represents a collection rather markedly uniform as to histology. It is safe to say that no series of cases has been so carefully scrutinized, criticized and classified as the present one.

While it was intended to limit the investigation to the pathologic aspect, the clinical and roentgenologic behavior of the tumor is so important that nothing less than a complete report will be of value. I entered into the work without preconceived ideas as to what the tumor was, and with imperfect knowledge as to its behavior. Outside the short historical section following, all the conclusions arrived at have come directly from the cases themselves, or from various opinions based on these cases.

HISTORY

Endotheliomas of bone have been described since 1866 when Lucké [3] described one resembling endothelioma. Hildebrandt [4] in 1890 collected those which had been reported in the German literature up to that time. Marckwald [5] in 1895 reported a case of multiple intravascular endo-

3. Lucké: Virchows Arch. f. path. Anat. **35**, 1866.

4. Hildebrandt: On Tubular Angiosarcoma or Endothelioma of Bone, Deutsch. Ztschr. f. Chir. **31**:263-281, 1890.

5. Marckwald: A Case of Multiple Intravascular Endothelioma in Most of the Bones of the Skeleton, Virchows Arch. f. path. Anat. **141**:128-152, 1895; also Centralbl. f. allg. Path. u. path. Anat. **5**:859-860, 1894.

thelioma in most of the bones of the skeleton, and in the same year Volkmann [6] included endothelioma of bone in a discussion of endotheliomas in general. Howard and Crile in 1905 [7] analyzed nineteen previously reported cases, adding four of their own, calling them endothelioma or perithelioma after Waldeyer's method. (The perithelioma of Waldeyer arises in the perivascular lymphatics.) Symmers and Vance,[8] Wells,[9] Ewing,[2] Morton and Duffy,[10] MacGuire and McWorther,[11] Greenough, Simmons and Harmer [12] and others have reported various cases. Ewing has done by far the most work on the tumor, and has summed up his cases several times.[13] No effort has been made to enumerate the cases reported. They have been in the past so confused with round cell sarcomas arising in the periosteum, parosteum and the medulla of bone that most of them must necessarily be left in oblivion.

ETIOLOGY

As in other tumors the final etiologic factor is unknown. Trauma plays an important but incalculable rôle, 40 per cent. of cases having a history of injury at the point involved at a time near enough to the onset of the tumor to be of some significance. Most subjects (73 per cent.) are males; most are young (80 per cent. under 30 years), the average age being 20 years; a few cases occur after 40; one patient was a woman of 60; the youngest patient was 3 years. Inflammation and marrow reaction (possibly to trauma) are closely linked with the origin and onset of the tumors. Twenty-two (40 per cent.) of the cases give a distinct history of having had signs pointing to inflammation as the cause of their trouble. A glance at the abstracts will show the large number diagnosed clinically and by roentgen-ray examination

6. Volkmann: On Endotheliolial Tumors, Deutsch. Ztschr. f. Chir. **41**:1-180, 1895.

7. Howard and Crile: A Contribution to the Knowledge of Endothelioma and Perithelioma of Bone, Ann. Surg. **42**:358, 1905.

8. Symmers, D., and Vance, M.: Multiple Primary Intravascular Hemangio-Endotheliomata of the Osseous System Associated with Symptoms of Multiple Myelomata, Am. J. M. Sc. **152**:28 (July) 1916.

9. Wells, H. G.: Relation of Multiple Vascular Tumors of Bone to Myeloma, Arch. Surg. **2**:435 (May) 1921.

10. Morton, J. J., and Duffy, W. C.: A Clinical and Pathological Study of Ten Bone Tumors, Arch. Surg. **7**:469 (Nov.) 1923.

11. MacGuire, C. J., and McWhorter, J. E.: Sarcoma of Bone: An Analysis of Fifty Cases, Arch. Surg. **9**:545 (Nov.) 1924.

12. Greenough, R. B.; Simmons, C. C., and Harmer, T. W.: Bone Sarcoma: An Analysis of the Cases Admitted to the Massachusetts General Hospital and the Collis P. Huntington Memorial Hospital from Jan. 1, 1911, to Jan. 1, 1921, J. Orthop. Surg. **3**:602-639 (Nov.) 1921.

13. Ewing, J.: A Review and Classification of Bone Sarcomas, Arch. Surg. **4**:485-533 (May) 1922.

as osteomyelitis or periostitis. Many have been operated on under such a diagnosis, and some have been reported by pathologists as inflammatory and not tumor. In many of the sections studied there are areas of inflammatory tissue, and some consist entirely of tissue that is indistinguishable from inflammation in bone. (It is understood that inflammation as used here is practically synonymous with tissue reaction and does not connote infection.) A very few were actually infected, but these followed operative incision or partial excision. Further evidence will be given later to confirm the opinion that not a few of these tumors begin with a reaction closely resembling inflammation in bone.

PATHOLOGY

The tumors are usually both central and cortical, situated near the middle of the shaft of the long bones. They are expansive and bone-destroying tumors, pushing the cortex outward, infiltrating it, sometimes pressing it apart and producing onion-like layers. Often the cortex is completely destroyed. There is not the bony shell that often covers the giant cell tumor, but there may be at first a layer of dense reactive or inflammatory bone laid down parallel with the shaft which, as the tumor grows, is in turn destroyed. There is no new bone formed in the tumor itself. The tumor tends to extend up and down the shaft, the medulla often being filled with tumor before much is evident from the outside. The periosteum may be roughened but not raised above the cortical bone as in subperiosteal tumor. The tumor is soft, very cellular; some are described as resembling brain tissue; others may be cystic with red jelly-like substance; still others are very vascular, but do not approach telangiectatic sarcoma. A coarse connective tissue usually divides the tumor into small lobules. It infiltrates the surrounding muscle and fascia, once free from the bone, but is usually rather well outlined by a thin pseudocapsule (Fig. 1). Metastases are most often in the skull and lungs, and here they form solid cellular tumors which actively destroy bone but do not produce new bone.

The type cell is round, oval or elongate, with little cytoplasm, or a clear or grayish, rarely lightly pink staining cytoplasm. In the diffuse cellular tumors the cells are so closely packed that they become polyhedral, and lie in a seeming syncytium formed by the cytoplasmic substance. In some tumors this resembles an intercellular substance, but does so because usually no definite limiting membrane can be made out. No true intercellular substance is formed. The nuclei are round or oval, often shaped like that of the endothelial cell and contain scattered chromatin material that does not lie close to the nuclear membrane as in lymphocytes; usually there is no nucleolus distinguishable. Mitoses are numerous, but an outstanding feature is the almost constant absence

of tumor giant cells or marked pleomorphism. The cells almost invariably contain only one nucleus (Figs. 2, 4, 12).

Two types are described by Ewing [13] as to histology: (1) angio-endothelioma and (2) diffuse. These may be recognized in the present series, and possibly a third type that is closely related to both of them is seen. The type cell as described above is the same in all of them.

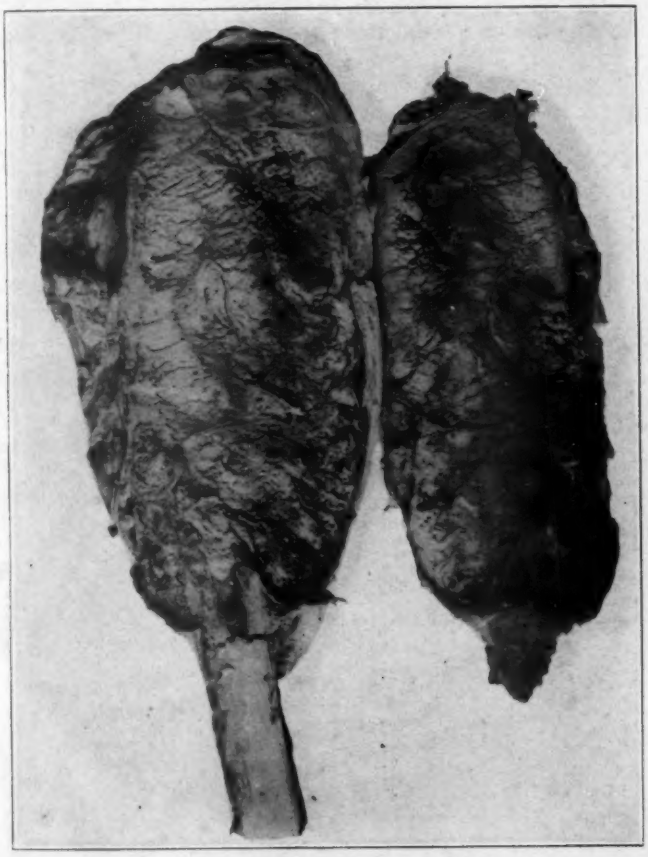

Fig. 1 (Case 54).—Cellular expansive tumor of medulla infiltrating and destroying cortex; lower end of fibula; gross specimen preserved by Dr. H. F. Hartwell, Massachusetts General Hospital, Boston.

1. Angio-endothelioma differentiates toward a vascular tissue, the cells sometimes becoming somewhat flattened, forming blood spaces and sinuses, approaching well-formed blood vessels, as seen in hemangio-endothelioma elsewhere. The cells may radiate from a central core, and perithelial structures are common. Spaces and clefts lined with tumor cells are frequent, and surrounding them there may be masses of cells

in no definitive arrangement. The whole tumor is usually divided into lobules by connective tissue septums (Fig. 3).

2. Diffuse endothelial myelomas appear in sections as sheets and masses of cells in large or small lobules, forming no definitive structure, but sometimes the cells are in rows, or in whorls, or form alveoli or rosette-like figures containing blood or other liquid in the centers (Fig. 7).

3. A reticular type (Figs. 4, 11, 12) verges into the angiomatous type on the one side, and into the diffuse type on the other. It consists

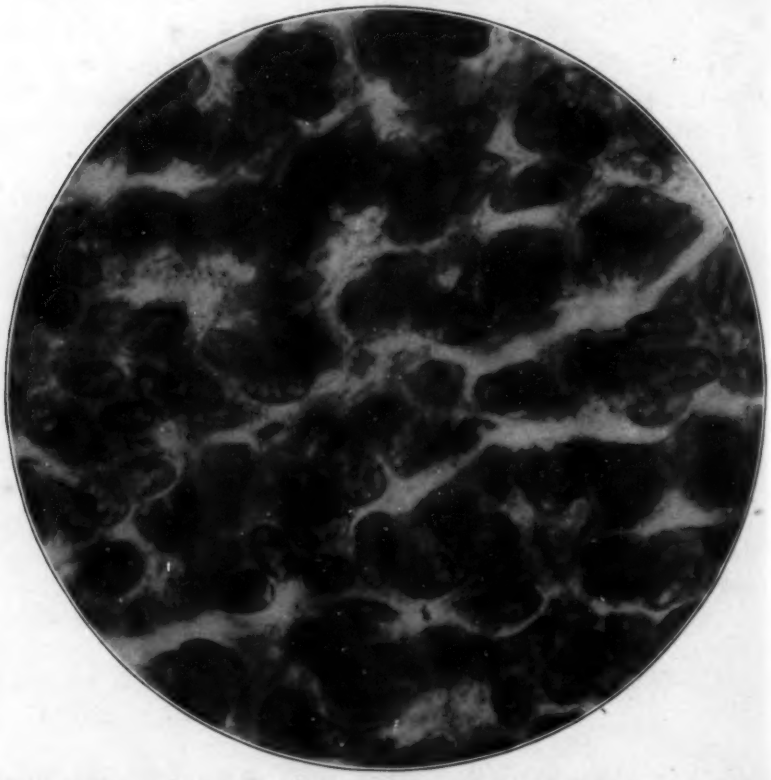

Fig. 2 (Case 29).—Type cell in diffuse endothelial myeloma: The nuclei resemble those of endothelial cells, having scattered chromatin and no distinguishable nucleoli; the cells are closely packed but tend to form small alveoli; × 850.

of the characteristic cell, the clear cytoplasm in this often being well marked, joining to form a lacy network, with fine cytoplasmic tendrils extending out to form small spaces, a counterpart of which may be seen in the reticulum of hyperactive bone marrow. It is possible that this may be the primitive, say, the true type, and that by differentiation and in response to factors such as pressure, tension and effect of treat-

ment an angiomatous structure may develop, or by pressure and rapid growth it may become closely packed and diffuse.

These three types merge so imperceptibly the one into another, often the three being found in the same tumor, that for histologic purposes they need not exist. For practical purposes the fact that the angiomatous type tends to be slightly less malignant, and the diffuse type more rapidly growing (it is diffuse because it is more rapidly growing), would be important in the prognosis of a case. This clinical distinction

Fig. 3 (Case 52).—Angiomatous or perithelioma type of endothelial myeloma, under low power.

is not sharp; it will be shown later how much reliance may be placed on it.

Two kinds of bone are encountered, viz., well formed developing bone in a myxomatous tissue indistinguishable from inflammatory or healing bone, and degenerating bone that is closely surrounded by tumor cells, but has lost all connection with its periosteum, having no osteoblastic layer. No tumor bone or cartilage is formed, and no collagen. There may be a sprinkling of plasma cells or, more often, none;

blood cells and bone marrow cells often complicate the picture, and in some undifferentiated tumors with poor fixation or thick sections it is sometimes extremely difficult to differentiate them from other kinds of myelomas. The type cell as described is a rather undifferentiated cell, and a totally undifferentiated fibrosarcoma cell, if such exists, may resemble it. One makes the histologic diagnosis of the diffuse type by its closely packed sheets of cells in lobules, and by eliminating all other tumors by the absence of any characteristic peculiar to them, as, for instance, fibrils and intercellular substance.

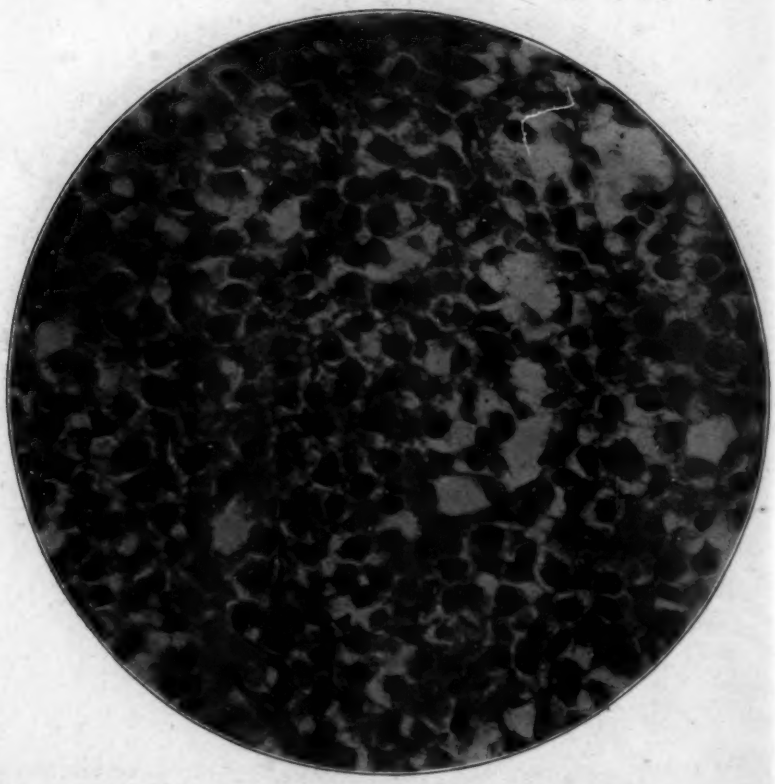

Fig. 4 (Case 50).—Reticular type of endothelial myeloma; cells with clear cytoplasm forming a reticular syncytium; × 700.

HISTOGENESIS

The interrelation of blood vessels and tumor cells in most sarcomas is so complex that, it seems to me, it is impossible by observation alone to say that a particular tumor arose from a particular kind of vessel, or from any vessel. Cases of endotheliomas have been reported as arising from blood vessels, lymph sinuses and lymph vessels in the walls of blood vessels. In the fifty-four cases studied here a large number of

stages in growth are represented, and a suggestion as to the origin of the tumor may, perhaps, be seen in some of them. Cases 44, 19, 5 and others were seen very early in their development, and Case 54 was studied carefully in an effort to find an area that might be taken as the earliest stage. In addition, sections from eleven other cases, Cases 50, 26, 25, 30, 19, 9, and four from the Warren Anatomical Museum of Harvard Medical School not included in this report were

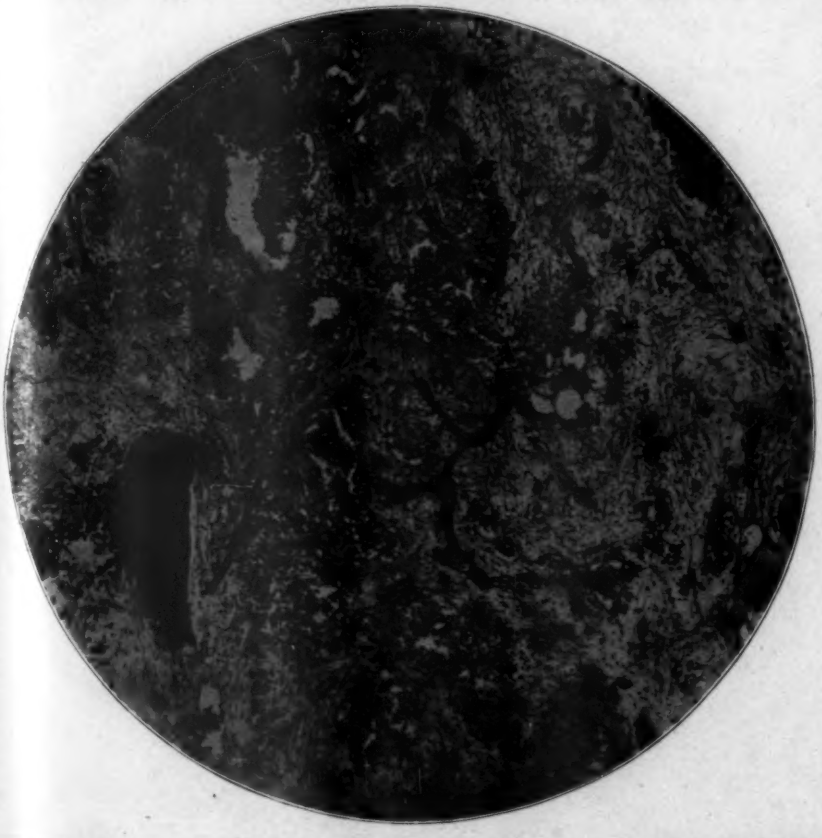

Fig. 5 (Case 44).—Cells apparently arising from the reticulum or capillaries between spicules of bone, under low power; they are forming and lining sinuses, making the picture that Ewing thinks shows the beginning of tumor. In the lower left center two kinds of cells may be distinguished, cells forming bone and tumor cells; the bone is reactive bone.

available for special staining and study. Case 44 (Fig. 5) is mentioned by Ewing as showing possibly the very beginning of the tumor. Here there are clumps of cells apparently arising from the sinuses or capillaries of the reticulum, forming and partly filling small spaces. However, Wright and Hartwell believe this to be an osteogenic sarcoma

because of the kind of developing bone present. Case 54 (Massachusetts General Hospital Case 1) has not this objection. The gross specimen of the tumor was lent to me by Dr. H. F. Hartwell, and a longitudinal section about 5 mm. thick was taken from the center of the tumor. This was cut into squares, and from each one several sections were taken. This gave sections from approximately every part of the tumor. They were stained with hematoxylin and eosin, Mallory's anilin connective tissue stain and phosphotungstic acid hematoxylin. In

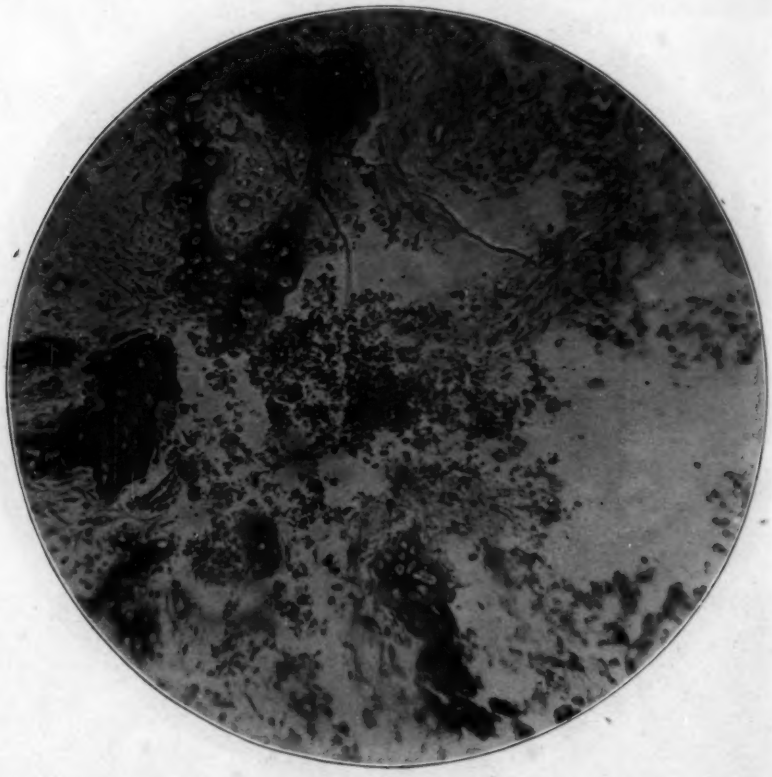

Fig. 6 (Case 54).—Cells arising from the reticulum in section from the cortex near the normal bone (Fig. 1) under low power; these cells can be distinguished from the cells that are forming reactive bone.

this tumor some developing bone is found, but it does not at all resemble tumor bone. Between the bony trabeculae of the cortex are numerous islands of tumor cells apparently arising from the reticulum (Fig. 6), in places so few that they seem indeed to be part of the reticulum. These are the same cells which in other places form a solid cellular tumor with a suggestion of a reticulated architecture (Fig. 7), and in other places are forming imperfect vascular sinuses containing normal

blood. This picture is seen in many others in the series, and shows a possible origin of cells that are indistinguishable from the cells forming the tumor.

It cannot be asserted positively, however, that this shows the beginning of the tumor. The hyperplasia of cells between cortical spicules may be a reaction easily accounted for by the presence of a tumor. This has been seen in about a third of the cases recorded, and is nearly always at the outer edge of the tumor. It is therefore often the part excised

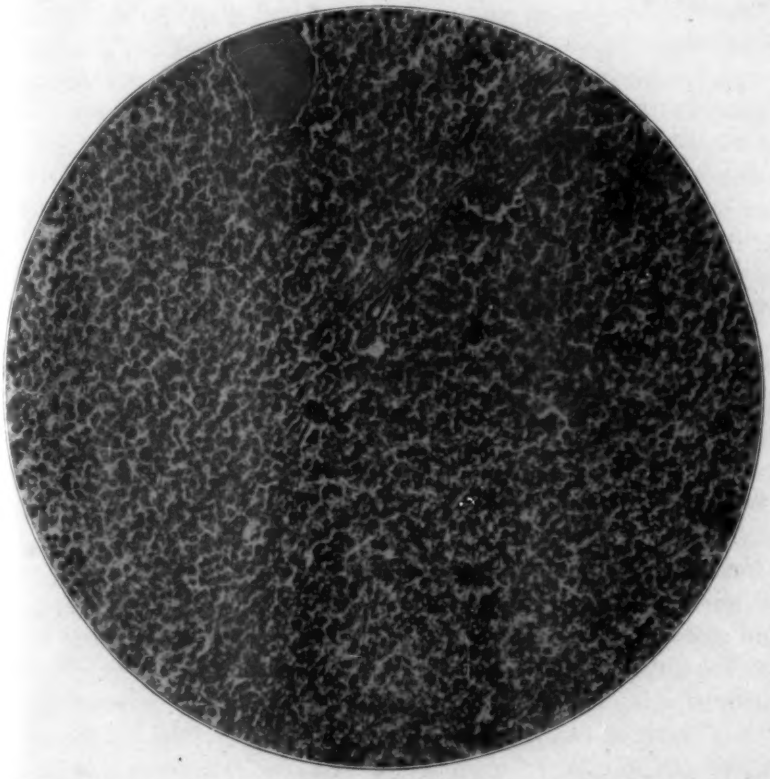

Fig. 7 (Case 54).—Section from center of tumor (Fig. 1) under low power; this shows the closely packed cells characteristic of the diffuse type of endothelial myeloma.

for diagnosis, and leads to the inevitable histologic diagnosis of inflammation. In the absence of definite tumor it cannot be otherwise interpreted.

None of the eleven tumors studied with special stains showed a collagenous intercellular substance, though in a few cases the reticulum formed was almost myxomatous in character. Closer inspection, however, showed that it was not myxomatous tissue, and it did not take the

connective tissue stain. With phosphotungstic acid hematoxylin it has been possible to determine sharp differences in the character of the bone forming cells and tumor cells. The former with their prominent nucleoli are seen to develop from elongate spindle cells, and have a denser cytoplasm than the tumor cells, the latter being polyhedral or rounded, with no nucleoli and clear cytoplasm. These have been seen side by side in the same section in a number of the tumors available for special staining.

An approximation that agrees with the foregoing evidence may be achieved by elimination, as has been done for other tumors. By studying and reporting cases many tumors have been sifted out automatically by time and the dissemination of knowledge as to their behavior. It is generally believed that the origin of the osteogenic sarcoma is in a cell closely related to, if not identical with, the fibroblast, which is capable of forming fibrous, cartilaginous, osteoid and osseous tissue. That this tumor is not an osteogenic sarcoma is inferred from the fact that it forms none of these substances. Its relation to the plasma cell myeloma is not understood, largely because the origin of multiple myeloma itself is not understood. A few contain plasma cells as well as other marrow cells, but most do not. Its behavior is not that of the plasmacytoma. The suggestion is made by Aschoff [14] that similar malignant tumors may arise from the reticulo-endothelial system, and Phemister, in remarking on Case 18 in this series, believes it arose from a reticular cell. Recently Foot [15] has reviewed the evidence in favor of malignant tumors of the reticulo-endothelial system, and describes one arising either in bone or in lymph nodes. This is quite apart from Ewing's contention, as his opinion is well known.

These opinions are supported by our knowledge of the origin of blood and connective tissue cells due to the work of Maximow,[16] Kiyono and Takamasu,[17] Ferrata,[18] Aschoff,[14] Sabin,[19] and many others. Maximow says that in early embryonic life a primitive mesenchyme cell forms a common cell that gives rise to fibroblasts, blood cells and the reticular cell, the latter forming the reticular syncytium of the bone

14. Aschoff, L.: Lectures on Pathology, New York, Paul G. Hoeber, 1924.

15. Foot, N. C.: Report of a Case of Malignant Endothelioma with Necropsy, J. M. Res. **44**:417-430 (June) 1924.

16. Maximow, A. A.: Relation of Blood Cells to Connective Tissue and Endothelium, Physiological Rev. **4**:533-563 (Oct.) 1924.

17. Kiyono, K., and Takemasu, N.: Acta scolae medicinalis Universitatas Imperialis in Kioto **3**, 1919, quoted by Aschoff (Footnote 14).

18. Ferrata, A.: Le emopatie, Milano, 1918, quoted from Maximow (Footnote 16).

19. Sabin, F. R.: On the Origin of the Cells of the Blood, Physiological Rev. **2**:38-69 (Jan.) 1922.

marrow and other blood forming organs. I believe it will be clear that endothelial myelomas do not belong to the blood-forming cell group (lymphocytomas, chloromas, myeloblastomas, leukemias, erythroblastomas, polycythemia); their differentiation from the fibroblastic group is less evident, but when the histology, clinical course and peculiarities as to metastasis are taken into account, it is more than suggestive that this tumor occupies a position midway between the two, and is not identical with either. "The reticular cell," says Sabin,[20] "differs from the fibroblasts . . . . in being more primitive, namely, in that the reticular fibrils remain within the cytoplasm of the cell throughout life." Whether the reticular and the endothelial cell are the same or, as the balance of opinion seems to suggest, are different cells cannot be discussed here. They are so nearly alike in function and appearance that they are spoken of as forming the reticulo-endothelial system. It is sufficient to note that both are capable of forming a reticulum, or spaces and sinuses, and of lining these sinuses (Fig. 8).

Whether the reticular cell may become a fibroblast is another question, which may possibly be answered in the affirmative. The step then to the osteoblast is generally conceded. One might therefore feel that many, if not all, medullary or endosteal osteogenic sarcomas, if there are such tumors, may arise from the reticular cell. One knows, of course, that the origin of all mesenchymal tumors must be very close. This fact of close relationship in origin does not prohibit their showing greatly differing characteristics in their differentiation. Complete discussions have been given recently by Aschoff,[14] Maximow [16] and Sabin [19] as to the origin of these cells.

Since it seems possible for this tumor to have arisen from the reticulo-endothelial elements in bone the name endothelial myeloma suggested by Ewing seems appropriate. Expressing as it does a bone marrow origin with endothelial characteristics this name sets it apart from all other myelomas and from osteogenic sarcomas.

CLINICAL COURSE

The bones involved have included particularly the long bones. There were ten in the tibia; seven in the humerus; six each in the femur and fibula; five in the clavicle; three each in the ulna, scapula and ilium; two each in the vertebrae, os calcis, metatarsals and ribs and one each in the ischium, radius and lower maxilla.

The onset was nearly always with pain as the first symptom, often pain and swelling; in only two cases was it accompanied with pathologic fracture. The intermittent pain, signs of inflammation and history of

20. Sabin (Footnote 19, p. 57).

trauma form a triad of signs that are characteristic. The following case has been selected as an example of a rather typical course:

The patient, a woman grocery clerk, aged 24 (No. 284, registered by Dr. R. B. Deane, Calgary, Canada), in February, 1922, fell on the ice and hurt her left knee. There was no immediate effect other than slight soreness lasting a few hours. Two or three weeks afterward when walking she felt a sharp pain in the same knee which made her limp for a few hours and then disappeared. It returned several times, lasting about a day and disappearing for a week or longer. The pain was dull, aching in character, not severe at first, but becoming worse with successive attacks. The swelling at first was insignificant, but for some months had increased, with variation from time to time. At the time of examination the pain and swelling were continuous.

Examination showed some left thigh wasting, no synovial swelling of the knee, but some subcutaneous thickening; there was no redness, but the joint was warmer than the other. There was marked localized tenderness over the inner tibial tuberosity to the medial side of the patellar tendon. The temperature was

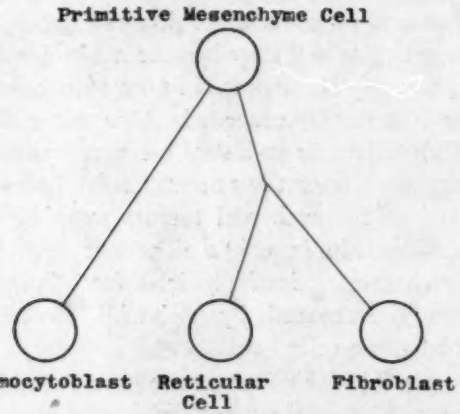

Fig. 8.—Line of descent of reticular cell, with relative positions of blood forming cell, reticular cell and fibroblast, adapted from Maximow, who attempts to correlate the various opinions as to the origin of these cells in a chart.[16]

98 degrees; pulse, 96, and respirations 24. The white cells totaled 13,000; polymorphonuclears, 74 per cent. The urine was negative and the Wassermann reaction was negative.

The first roentgenogram (Fig. 9) showed slight roughening of the periosteum and a rarefied area in the medulla, and under the tentative diagnosis of Brodie's abscess, an exploratory operation was done in October, 1922. At this time, the cortex was somewhat roughened, and in the underlying medulla there was a cavity the "size of a walnut" containing pale granulation tissue. The cavity was scraped, filled with a muscle flap, and the wound closed. It healed by first intention. The laboratory reported the cavity contents to consist of pus cells, no tuberculosis, and no organisms on cultivation. The diagnosis of inflammation was strengthened by the fact that for twenty years the patient had had a running ear.

The patient was readmitted to the hospital, Jan. 8, 1923, the knee now being very painful and more swollen. The roentgen-ray examination showed a tumor that was considered to be of cystic nature. A second operation was done to

relieve tension, the cavity being lightly stuffed with gauze. The laboratory report on the cavity contents was inflammation. Still believing that the condition was secondary to the ear infection, a radical mastoid operation was done. The tumor continued to grow rapidly, and another picture showed a central tumor (Fig. 10). Dr. Deane says: "considering it a central growth I called it a myeloma in consonance with English teaching that, for practical purposes, primary endosteal malignant tumors do not exist." Although the tumor was

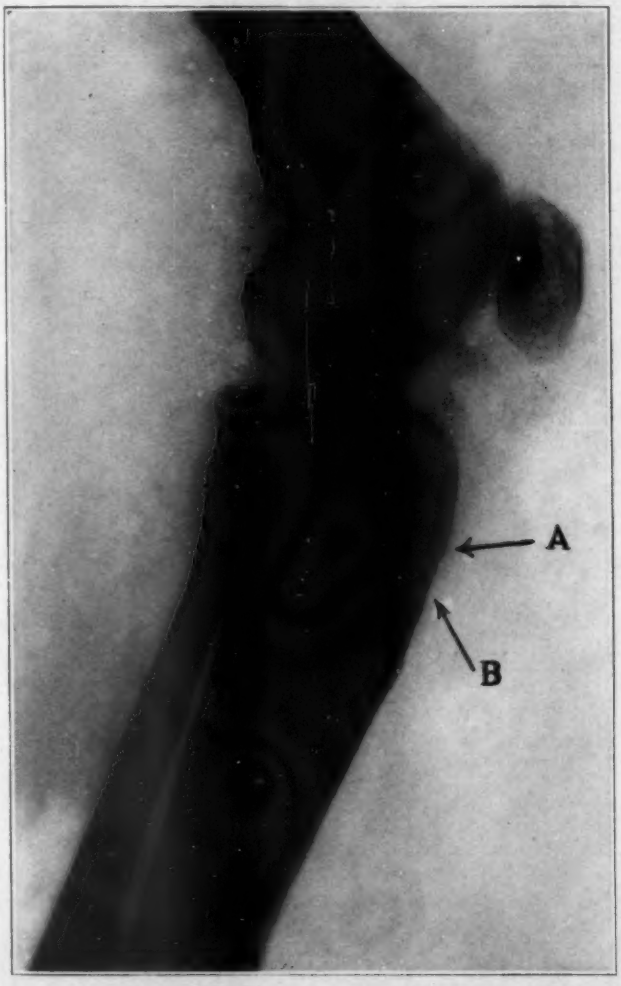

Fig. 9 (Case 19).—Beginning of tumor in medulla and cortex resembling inflammation; *A*, bone rarefaction; *B*, small circumscribed area of lessened density at medullary margin.

growing very rapidly, the girl's ear condition did not permit of intervention until March 27, 1923. Operation at this time disclosed a large, very vascular solid tumor, dull red, encapsulated and not infiltrating the soft parts, springing apparently from the marrow cavity. Frozen section diagnosis was malignancy,

and amputation was done. The wound healed without complication, and the patient was discharged.

In October, 1923, Dr. Deane reported that the patient had gained much in weight, felt very well, was wearing an artificial leg, and meant to return to work. April 7, 1925, the patient was earning her living as a telephone operator and felt well, having gained more in weight.

There are six pictures of the tibia included. The first one shows slight roughening of the periosteum, with a medullary rarefaction rather circumscribed. Successive pictures show a progressive tumor beginning in the medulla, eroding through the cortex, and appearing on the outside as a soft mass. The periosteum is not raised as in osteogenic sarcoma, and the few denser specks that suggest bone are scattered near the cortex, and probably are remains of normal bone (Fig. 10).

Fig. 10 (Case 19).—Soft bone destroying tumor, not often located at end of bone, before amputation; the picture is distorted by operation.

The tumor consisted of a very cellular reticulated tissue, the cells rounded or polyhedral, with clear cytoplasm and densely staining nuclei in which the chromatin was scattered and no nucleoli could be distinguished. These cells were infiltrating fascia, being only partly covered by a pseudocapsule of fibrous tissue and muscle in which tumor cells were found. The tumor was divided into lobules by fibrous tissue septums. The cells joined in many places forming a lacy network by anastomosing cytoplasmic tendrils, but no intercellular substance was formed. A few spicules of dissolving bone were present, but no new bone. An occasional area of necrosis was seen (Figs. 11 and 12).

Fig. 11 (Case 19).—Reticular type of tumor, the cells forming a lacy network and sinusoids, under low power.

The foregoing history was repeated many times in the cases reported. These case reports will show that the following points in this history are characteristic: 1. The trauma is so closely related to the onset that it must be considered as a causative factor. 2. The long period of pain, intermittent in character, before the condition is thought to be serious enough to warrant calling in a physician. 3. The swelling progressing intermittently. 4. The roentgen-ray and clinical diagnosis of osteomyelitis. 5. The finding at operation of a tumor suggesting granulation

tissue, and the pathologic reports sustaining the diagnosis. 6. The recurrence and rapid growth.

There are three ways in which such a history may end: 1. Amputation is done, and with or without radium and roentgen-ray treatment the patient will recover and live for an indefinite period. 2. The tumor may recur, or even metastasize to other bones, and by radiation the condition will be held in control for a period of from a year to fifteen years (as long a period as is covered by these cases). 3. The tumor will recur in the skull, in other bones and in the lungs, be controlled by

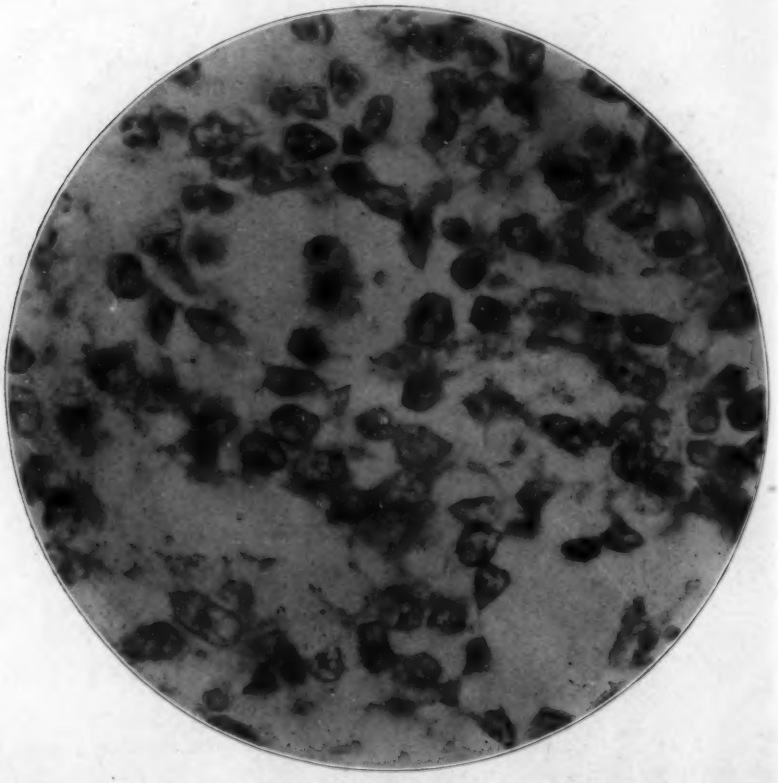

Fig. 12 (Case 19).—Cells of type case, showing clear cytoplasm and anastomosing cells forming spaces; in most of the cells the chromatin is so scattered that nucleoli cannot be distinguished; × 800.

radium or roentgen ray for a short time but eventuate in death, usually within two years.

Variations from this picture are not numerous. The tumor may arise suddenly, metastasize early, and in spite of treatment end fatally in as short a time as six months. Or the patient may present himself with lung metastases, and, because the case is considered hopeless, little

is done, and the patient will die within two years, usually with multiple bone tumors.

MULTIPLICITY

Multiple bone tumors were present when the patient was first seen in only three cases (Cases 51, 5 and 35). Practically all those who died had multiple bone metastases, constantly in the skull, occasionally in the vertebrae and long bones, and almost always in the lungs. Metastases to the soft organs, besides the lungs, are infrequent. Only two are recorded as metastasizing to the liver, four to the lymph glands, two to the spleen, and two to the kidneys. This is the least accurate finding in the series, and is obviously too low, as necropsies were done in less than a third of the cases. But what seems of significance is the fact that the tumors are not at first multiple, but become multiple only after periods of months or years.

A glance at the case reports will show how closely these follow the usual course of a malignant tumor: at first solitary, later showing up usually in only one bone (the skull) or in the lungs, and, often enough to set it apart from other tumors, in several bones. These metastases occur anywhere from a few months to one year (Cases 6, 26, 2 and others) or three years (311) after the original tumor. This, I think, places the tumor apart from tumors and conditions arising from the blood cells, and perhaps from multiple myeloma, which may be regarded as tumors or systemic affections of the hemopoietic tissues. The predilection to metastasize to bone likewise places it apart from osteogenic sarcoma.

DIAGNOSIS

The diagnosis must be made from osteogenic sarcoma, chronic inflammation, metastatic tumors and multiple myeloma. The chance of confusing endothelial myeloma with benign giant cell tumor is considered almost nil. The typical osteogenic sarcoma and acute inflammations in bone offer no difficulty, but there are borderline cases in which careful correlation of all signs and symptoms is necessary. While the roentgenogram is the most important single factor in a diagnosis, it is an error to rely solely on its interpretation. I have tried to present here what I believe to be a clinical entity, with a history, course and outcome that are no more confused than those of many diseases that are diagnosed correctly from their symptoms and physical signs. It is therefore necessary to have as complete a history and examination (including blood and urine) in tumor cases as in any other disease not subject to roentgen-ray examination.

The roentgenogram in endothelial myeloma will usually show a tumor of the shaft of a long bone, most often in the center, infrequently near the end. The tumor is usually widespread, occupying over half

the shaft, expanding, destroying and invading the cortex. It begins apparently in both the medulla and the cortex, and very early the periosteum shows invasion, with a roughening or fragmentation which is confused with the picture of periostitis. As the tumor grows the cortex dissolves, and one does not see a raised periosteum as in subperiosteal osteogenic sarcoma, for it has long since been invaded and destroyed

Fig. 13 (Case 32).—Typical endothelial myeloma—a soft tumor arising in the medulla, expanding and infiltrating the cortex, occupying a large part of the shaft.

by the tumor. The shaft does not retain its density and structure as it does in nearly all osteogenic sarcomas. Rarely, new bone is formed, and this is laid down parallel with the shaft, not radiating, though occasionally radiating spicules may be seen. When it also involves the

soft parts it is usually well outlined. The edges may be scalloped owing to the nodular surface of the tumor. The accompanying table points out some of the differences between endothelial myeloma and osteogenic sarcoma as seen in the roentgenogram (Figs. 13, 14 and 15).

Metastatic tumors in bone occur in the extremes of life, as a rule. In patients past middle age carcinoma is the only one of practical importance. The age and the finding of a primary tumor elsewhere differentiates it. After 40 years of age a tumor in bone is most often either a metastatic tumor or multiple myeloma. Before the age of 10 many tumors resulting from cell rests, inclusions and displacements are found apparently anywhere in the body. These occasionally metastasize or even arise in bone, the most frequent metastases probably being from neuroblastomas from the suprarenal and the sympathetic ganglions. These are comparatively rare tumors in bone, but should be thought of when confronted with an atypical bone neoplasm.

Roentgenographic Differences Between Endothelial Myeloma and Osteogenic Sarcoma

Endothelial Myeloma	Osteogenic Sarcoma
Occurs usually in the shaft	Usually near ends
Osteolytic	Osteoblastic
Widens the shaft	Does not widen and may narrow
Involves more than one-half the bone	Involves less than one-half
Destroys cortex in vertical, linear manner	Destroys cortex little, and then from side to side
New bone, if any, parallel with shaft	New bone radiating
Late, multiple in bones	Not often multiple

Multiple myeloma usually causes a more definite and sharply outlined area of bone destruction, often forms multiple nodules in the same bone, and much more frequently than endothelial myeloma is multiple in other bones almost from the onset. It tends to limit itself to the bone marrow, very rarely infiltrates the soft tissues, and metastasis to the lungs is unusual. Bence-Jones protein occurs in about half the cases, and this is rarely present in endothelial myeloma. The age of incidence is of distinct help, multiple myelomas occurring chiefly after the age of 35.

Chronic osteomyelitis, osteitis, periostitis and abscess form the group from which it will be the most difficult to differentiate endothelial myeloma in its early stage. Ewing [13] says: "It may be of interest to note that competent observers firmly maintained that some of my cases were osteomyelitis, while one patient was persistently treated with arsphenamin," but that "the diagnosis can generally be made on the clinical history, the peculiar roentgenogram, and the early response to radium." The blood picture is given in very few of the cases recorded here, but there may be an increase in the number of cells to 12,000 or

slightly above, the cells maintaining usually their normal ratio. Signs of local inflammation are frequent, and there may be a slight rise in temperature in endothelial myeloma. Occasionally the advent of metastases is accompanied by a distinct febrile reaction. Slight fever, an aching bone, a slight or no leukocytosis, with a history of insidious onset and

Fig. 14 (Case 54).—Most frequent situation and appearance of well developed tumor, showing soft tissues extensively invaded; considerable detail of the tumor has been lost by reduction from a large roentgenogram.

intermittent pain, should lead to the diagnosis of tumor rather than to osteomyelitis. I believe that no diagnosis of chronic osteomyelitis should be made before ruling out the possibility of a tumor. Excision of a piece for diagnosis, though not always accompanied by disaster, is sub-

ject to the same objections here as in any other malignant tumor, and the radium therapeutic test suggested by Ewing and the roentgenogram should be the final factors in the diagnosis.[21]

PROGNOSIS AND TREATMENT

Twenty-six of the fifty-four subjects are dead, but in two death was not due directly to the tumor. In the twenty-four who died from the tumor the average duration of life from the onset was about nineteen months, or somewhat longer than the time covered by osteogenic sarcoma, the only recent figure I have seen for the latter being about sixteen months (estimated from the case reports of Greenough, Simmons and Harmer[12]). The average duration of endothelial myeloma in those still living is about four and a half years, and the average duration in all, living and dead, is above three years. One patient is alive fifteen years after the last treatment (Case 1); one lived nine years before dying of another illness (Case 29), and fifteen are living four years after the onset of the disease. One sees that, as a whole, endothelial myeloma allows a longer term of life than most malignant tumors. Figures as to cures when so many patients are still under treatment are, of course, of little value, but counting those living more than four years after the last treatment as possibly cured, the percentage is about eleven.

The type of tumor may have something to do with the duration. I have already indicated that histologically it is frequently difficult to differentiate sharply the angiomatous type from the diffuse, but in some the angiomatous character is striking. It follows that this type which shows the greatest differentiation, in common with other tumors, should be the least malignant. Sixty per cent. of those which might be called angiomatous are still alive, while only 43 per cent. having a diffuse character are still living. I cannot find that the age of incidence enters into the formation of type to a considerable degree as Ewing[12]

21. Recent publications on the differential diagnosis of bone tumors by roentgen ray are: Codman, E. A.: The Nomenclature Used by the Registry of Bone Sarcoma, Am. J. Roentgenol. **13**:105-126 (Feb.) 1925. Meyerding, H. W.: Value of Roentgen Ray in Diagnosis and Prognosis of Sarcoma of Long Bones, J. Bone & Joint Surg. **5**:323-330 (April) 1923. Bloodgood, J. C.: Differential Diagnosis of Periosteal Bone Lesions, Radiology **3**:432-433 (Nov.) 1924. Nichols, B. H.: Roentgen Diagnosis of the More Important Tumors of the Long Bones, Surg., Gynec. & Obst. **35**:301-304 (Sept.) 1922. Baetjer, F. H.: Differential Diagnosis of Bone Tumors, Am. J. Roentgenol. **5**:260 (May) 1918. It must be mentioned that the paper by Kolodny (Kolodny, A. A.: A Case of Primary Multiple Endothelioma of Bone with Special Emphasis on its Roentgenologic Features, Arch. Surg. **9**:636-646 [Nov.] 1924) is misleading, the peculiar tumor reported by him having no feature in common with endothelial myeloma.

and Howard and Crile [7] have indicated. The average age of those having the angiomatous type is 21 and those with the diffuse, 19.

The treatment has the greatest influence on the prognosis. Here radium is the first thought, with the roentgen ray a close second. Ewing has insisted that radium and roentgen ray be tried in all these and doubtful borderline cases before any other treatment. The rapidity

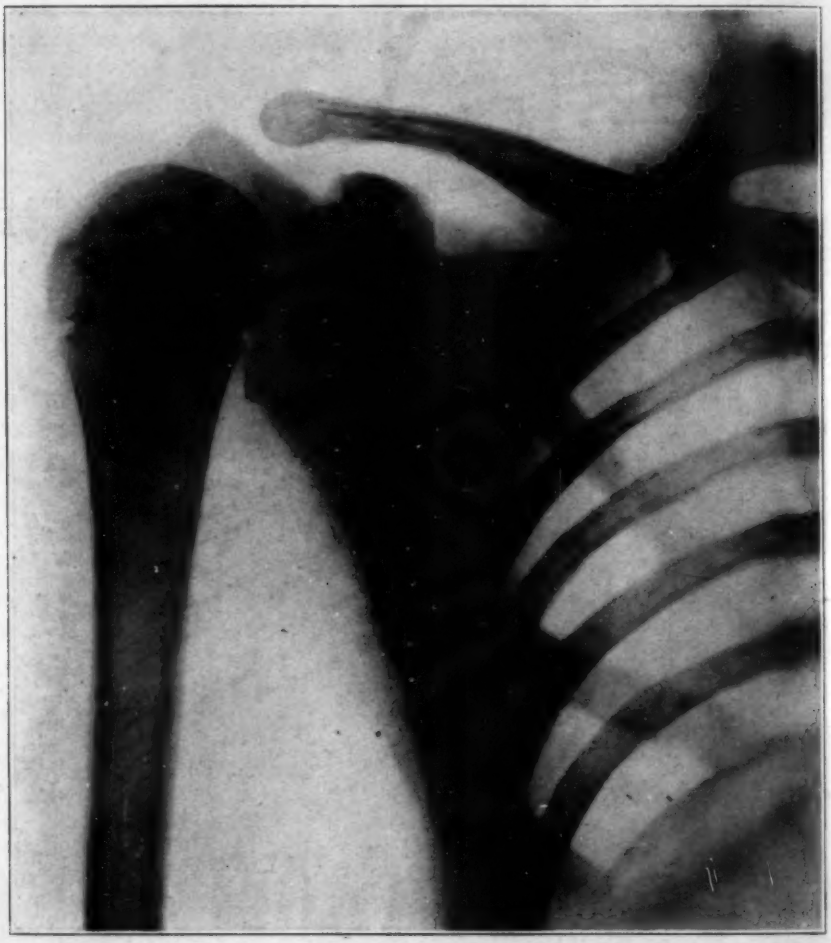

Fig. 15 (Case 2).—Usual appearance in clavicle.

with which most endothelial myelomas melt down under radium, in contrast to osteogenic sarcoma, constitutes a means of differentiation from the latter tumor. Only one patient in this series (Case 3) has been treated with radium alone without surgery of any kind, and he is living four years after beginning treatment. The case reports indicate that many have been greatly improved, if not cured, by roentgen ray or

radium or both. However, a series of cases in which treatment was given by these methods only is lacking, and it will not be known whether they are curative or palliative until such is forthcoming.

It is true that in this series the patients that have lived the longest have been operated on, either by excision of the bone containing the tumor or by amputation. But these patients have also in most cases been treated with roentgen ray or radium. Many cases show that the tumor withstands an unusual amount of surgery without becoming rapidly fatal. Most have had a combination of radium, roentgen ray and incision or excision, and many also have had Coley's mixed streptococcus and *Bacillus prodigiosus* toxins, so it is difficult to say which has been of most benefit. Ewing urges against amputation that other primary growths may appear in the skull or in other bones, and so amputation may be of no permanent value. I cannot make a definite statement on this question, but believe that the evidence in these cases points to the secondary growth as actual metastases rather than multiple primary neoplasms, and therefore that amputation is not contraindicated.

Coley's toxin seems to have been of some benefit in several cases, whether temporary or permanent cannot be determined, as no case is included in which it alone was used. It is only of academic interest to note that gonococcus vaccine caused complete remission of symptoms for a year in one case (Case 4). I can see no advantage in subjecting a patient to severe protein shock when roentgen ray or radium will produce the same or better results with less discomfort.

Finally it is urged that endothelial myeloma should not be looked on as hopelessly fatal from the start; rather that here is a tumor that presents the opportunity to use radium, the roentgen ray, and intelligent surgical judgment when they are likely to be attended with considerable success; and that a consistent and persistent attack on a terrible disease will frequently control it temporarily, and, it is believed in a gratifying number of cases, permanently.

SUMMARY

There have been sixty-seven cases of Ewing's tumor, in this paper designated endothelial myeloma, recorded in the Registry of Bone Sarcoma of the American College of Surgeons. This constitutes about 10 per cent. of all the bone tumors registered, and they are considered important enough clinically and pathologically to report in full. The belief that these form an entity separable from osteogenic sarcoma is borne out by the characteristics here emphasized, namely, their almost constant location in the shafts of the long bones and in flat bones where osteogenic sarcoma seldom occurs, their peculiar morphology, the type cell being easily distinguished from the osteoblast in most cases, and their susceptibility to radium and roentgen-ray treatment. The cells do not

form an intercellular substance that will stain with the dyes used to differentiate collagen, bone and cartilage. At the same time the cells are separable from those arising from the primitive hemocytoblast, and are considered therefore to be different from other various forms of myeloma which presumably arise from that cell. They resemble other myelomas by their predilection to metastasize to other bones.

They occur in children mainly, and many of them are preceded by trauma and by signs of inflammation, apparently resulting from the trauma, this inflammatory reaction passing so imperceptibly into malignant disease that the two seem inextricably associated in the early stage.

Histologically they may be divided into angiomatous, reticular and diffuse, the first perhaps somewhat less malignant, being furthest differentiated, the last the most malignant. The reticular type is considered the parent type, the other two being variations of this caused by location and differences in rate of growth. Several tumors studied showed the tumor apparently arising from the reticulum of the bone, and this with the evidence presented concerning the embryologic development of the reticular cell from a primitive mesenchyme cell seems to indicate that its origin is in the cells of the reticulo-endothelium of the bone marrow. Because it is desired to express this origin in the name, it has been called endothelial myeloma, thus sharply distinguishing it from all other bone and bone marrow tumors.

Several important characteristics almost constantly associated with the tumor are the slow development with intermittent pain, swelling that may recede only to return and to become progressive and the distressingly frequent confusion with chronic osteomyelitis clinically, roentgenologically and even occasionally histologically. But it is possible to diagnose it in most cases by correlation of the history and physical signs with a rather typical roentgenographic picture. As a final distinguishing point, the therapeutic radium or roentgen-ray test is advocated, this tumor, in contrast to osteogenic sarcoma, usually melting away under the influence of these forces.

Contrary to the opinion of Ewing and others, it is thought that endothelial myeloma arises as a solitary tumor, the multiple tumors appearing as actual metastases, and for this reason it is believed that amputation in the early stage is a form of treatment to be considered, though apparently radium has cured several cases.

The prognosis, with a combination of surgery and irradiation, is not always death. Patients have lived for five years or longer, one sixteen years, after amputation, and many who have been treated by a combination of surgery, radium, roentgen-ray and sometimes Coley's toxins, are living over three years after the onset of the disease. The prognosis seems distinctly better than that of osteogenic sarcoma and other myelomas, and for this reason it is urged that these be considered special cases in which, by energetic measures, a permanent cure may be possible.

REPORT OF CASES

In the following cases there are several tumors in which the diagnosis has not been made from the histology alone. There are instances in which diagnoses of inflammation or other tumor have been made by competent pathologists. It must be remembered that in these cases the pathologist has made a decision under protest, as the section that he saw was very poor, or was taken from a part of the tumor that was not characteristic of the whole. It seems necessary still to impress the surgeon and pathologist that one section from any tumor is of little value; that a tumor must be studied from all angles and from many parts to make a decision worth while. The fact that some of the tumors reported here were diagnosed from a single section, and that often a poor one, detracts from the value of the whole. The doubtful ones, however, have not been included. It will be seen that, with the exception of one or two, they form a rather characteristic group.

CASE 1.—*Living five years after last treatment.* A man, aged 21, with tumor of the femur (No. 398, registered by Dr. W. B. Coley), stated that the onset had been in February, 1909, with pain and moderate swelling. The roentgen-ray diagnosis was possibly periostitis. Excision was done in August, 1909. On recurrence, he was treated with Coley's toxin; and amputation was done in December, 1909. No roentgenograms were made. On histologic examination there were medium size round cells with vesicular nuclei and a small amount of clear cytoplasm. There were many blood vessels which lay in intimate contact with the cells that radiate from the vessel walls in a manner that suggested their having originated from them. The diagnoses were: Ewing, "endothelial myeloma;" Mallory, "malignant tumor, rapidly growing, probably endothelioblastoma;" Wright and Hartwell, "osteogenic sarcoma;" Graham, "periosteal sarcoma," and Cutler, "malignant tumor."

April, 1925, the patient was well. The duration was sixteen years after onset; fifteen years, four months after amputation.

CASE 2.—A boy, aged 13, with swelling of the clavicle (No. 28, registered by Dr. A. J. Hosmer, Salt Lake City), received the roentgen-ray diagnosis of sarcoma. Excision was done. Recurrence followed in a lymph node (?) a year later; this was excised. Roentgen-ray treatments also were given.

On histologic examination there were round to oval cells characteristic of Ewing's tumor and here certainly resembling endothelial cells; the cells formed blood vessels and vessel-like spaces; it was termed an angio-endothelioma. Hemangio-endothelioma was the diagnosis of Wolbach, Mallory, Speese and Stiles.

The patient was well in April, 1925. The duration was seven years after onset, and about five and a half years after the last treatment.

CASE 3.—*Living four years after last treatment.* A man, aged 30, with myeloma of the humerus (No. 246, registered by Dr. J. C. Bloodgood), suffered the onset about August, 1918, with pain; more than a year later a swelling appeared. The roentgen-ray diagnosis of Drs. Bloodgood and Max Kahn was periosteal sarcoma; of Drs. Ewing and Codman, probable endothelial myeloma.

Roentgen-ray examination showed a fusiform swelling of the shaft of the humerus and swelling of the surrounding soft parts; there was considerable bone

destruction, the medulla and the cortex being mottled. The roentgenogram seemed typical of Ewing's tumor. Radium treatment was given, with complete recovery. No operation was performed.

In October, 1924, the patient was well. The duration was six years after onset, four years after beginning treatment. No sections were taken. The case is included here as an example of apparent cure by radium.

CASE 4.—A man, aged 30, with myeloma of the tibia (No. 311, registered by Dr. J. C. Bloodgood), suffered the onset in 1916 with pain; recovery followed. Three months later there was pain near or in the knee joint which lasted for three days and was then intermittent. An operation was performed in January, 1917, five months after the onset. The surgical diagnosis was inflammation. No relief was given.

The patient was treated (in San Francisco) with "antigonococcus" serum, baking and massage. He was free from pain for one year. Recurrence followed. A second operation was performed three years after the first. The roentgen-ray diagnosis was osteomyelitis. The wound never healed. Amputation was done, Nov. 20, 1920. In May, 1924, the patient was well.

On histologic examination, most sections showed inflammatory granulation tissue; one a cellular tumor (round cells with no intercellular substance) infiltrating the tissue. The duration was eight years after onset, four years after amputation.

CASE 5.—A woman, aged 30, with myeloma of the clavicle (No. 196, registered by Memorial Hospital Clinic, New York), suffered the onset about July, 1920, with stiff neck, followed by tumor. Roentgen-ray examination showed the third and fifth cervical vertebrae also to be involved. The diagnosis was endothelial myeloma. March 28, 1921, a piece was excised for diagnosis. The patient was completely ataxic, keeping to bed. Radium treatment was given with marked improvement. Roentgen-ray examination showed a destructive tumor of the clavicle and vertebrae without bone formation.

On histologic examination, round cells packed in masses and sheets, some in rows, invading the muscle and fascia were seen; in places there was a reticulated structure with sinus formation, the cells joining to form spaces and lining spaces, some of which contained blood. The patient was well and working in April, 1925. The duration from the onset was nearly five years; from the beginning of the treatment, four years.

CASE 6.—*Living three years after last treatment.* A boy, aged 6 years, with myeloma of the femur (No. 348, registered by W. B. Coley), suffered the onset in 1916 shortly after a fall, with a tumor as the first symptom. Roentgen-ray examination showed a tumor destroying the bone. In August, 1917, amputation was done. The pathologic report was round cell sarcoma. In October, 1918, there were metastases to the skull, treated with Coley's toxin with recovery. In April, 1920, there were metastases in the occiput. Roentgen-ray and radium treatments were given, with recovery. In April, 1922, there had been no recurrence; radium was given as a prophylactic. In April, 1925, the patient was well.

On histologic examination, round to oval cells in closely packed masses in a reticulated stroma, and blood throughout, were seen. Many white blood cells complicated the picture. The final report was that the patient was well about nine years after the onset; eight years after the amputation; five years after the last recurrence, and three years after the last treatment.

CASE 7.—A girl, aged 7 years, with myeloma of the tibia (No. 185, registered by Dr. W. B. Coley), suffered from pain and swelling. The roentgen-ray diag-

nosis was sarcoma. Roentgen-ray treatment caused improvement. Recurrence followed. An operation was performed (kind unknown). Amputation was done, and radium and Coley's toxin were used. Roentgen-ray examination showed the tibia widened and honeycombed throughout, the bone indistinct, the periosteum elevated.

Histologic examination revealed round cells with somewhat denser staining nuclei than usual, arranged irregularly. There was some new bone formation which resembles callus bone rather than tumor bone; the cells and the disposition resembled myeloma. The patient was well six years after onset.

CASE 8.—A girl, aged 9 years, had myeloma of the lower maxilla (No. 294, registered by Dr. Allen Graham, Lakeside Hospital, Cleveland). In September, 1920, the illness had begun with swelling of the jaw; a tooth was extracted by a dentist with temporary relief; later, the jaw was lanced twice with no relief. The roentgen-ray diagnosis at the outpatient department was osteomyelitis. Excision and curettage were done. Feb. 18, 1921, the pathologic diagnosis was small round cell sarcoma. Radium and roentgen-ray treatments were given. The wound healed slowly but finally. March 3, 1923, the patient was discharged from the outpatient department with the note: "Apparently a complete cure. There is firm union of the jaw. No evidence of recurrence. No palpable glands. To return in three months."

Histologic examination revealed round cells in a very vascular and hemorrhagic tissue; the cells resembled the Ewing type, but the arrangement was without character. In October, 1924, the patient was well. The duration from the onset was four years; from operation, three years, eight months.

CASE 9.—A female, age not given, had myeloma of the scapula and clavicle (No. 137, registered by Dr. J. C. Bloodgood). In April, 1920, a painful swelling had appeared of which the duration was unknown. The roentgen-ray diagnosis was sarcoma. In June, 1920, the scapula and the outer end of the clavicle were excised by Dr. A. J. Buist, Charleston, S. C. Sept. 26, 1920, all of the clavicle was removed on account of the painful swelling. Roentgen-ray treatments were given after the first and the second operation. Roentgen-ray examination showed a destructive tumor of the spine of the scapula.

Poor sections were secured for histologic examination but part of the tumor resembled a vascular, cellular tumor not inconsistent with Ewing's tumor. In May, 1924, the patient was well. The duration from the onset was four years; from the last operation, three years, eight months.

CASE 10.—A woman, aged 60, had myeloma of the ulna (No. 141, registered by Dr. A. J. Ochsner, Chicago). The onset was in September, 1921, with intermittent pain, lasting about three days, coming at weekly intervals and followed by swelling of the forearm and wrist. The roentgen-ray diagnosis was possible periosteal sarcoma. This was curetted, Dec. 12, 1921. There was a tumor of the medulla, cortex and periosteum. Coley's toxin and roentgen-ray treatment were given. Roentgen-ray examination showed a diffuse tumor of the upper shaft with no new bone formation.

Histologic examination revealed round cells invading the muscle and fascia. There was no intercellular substance. The section was poor, and Wright, Mallory and Wolbach did not make a diagnosis beyond malignant tumor, but Ewing called it diffuse endothelioma. The patient was well in March, 1925. The duration from the onset was three years, six months; from operation, three years, three months.

CASE 11.—*Living three years after onset.* A man, aged 38, had myeloma of the humerus (No. 241, registered by Dr. H. Flecker, Melbourne, Australia). The pain had been general in the bones and the joints, and had also been local; then swelling had appeared. A piece was excised for diagnosis, which was sarcoma. Roentgen-ray treatments were begun in 1920. Roentgen-ray examination showed a diffuse tumor involving the length of the humerus and the soft parts; the periosteum was rough and the cortex partly destroyed.

The sections for histologic examination were poor; they revealed round cells embedded in a lacy network of substance. The patient was well in August, 1924. The duration was four years after onset.

CASE 12.—A man, aged 50, with a metatarsal myeloma (No. 560, registered by Dr. B. L. Coley, New York), about March, 1921, twisted his foot. There was pain and swelling, which left in three weeks. The pain and swelling recurred, the swelling varying in size until May, 1924, when it began to enlarge rapidly. Examination showed a tumor of the dorsum provisionally diagnosed myxoma. Sept. 25, 1924, roentgen-ray examination showed the shaft of the third metatarsal completely destroyed. There was no local bone production. Sept. 25, 1924, the tumor and a wide surrounding area were removed. Dr. Ewing's diagnosis was endothelioma of bone. Radium treatment was given, with an uneventful recovery.

Histologic examination revealed round cells forming a loose reticulated structure with many vascular channels lined with endothelium. The diagnosis was angio-endothelioma. The patient was well in April, 1925. The duration from the onset was four years; from the operation and the radium treatment, six months.

CASE 13.—A boy, aged 11 years, had myeloma of the third rib (No. 364, registered by Dr. J. Ewing). In the early summer of 1921 he had a fall; three months later a tumor appeared in the axilla, increasing in size. Roentgen-ray examination showed a huge tumor of the left side of the chest involving the third rib. A piece was excised for diagnosis. Ewing's diagnosis was: "a true perithelioma or angiosarcoma; structurally it looks like endothelioma." Roentgen-ray treatments were given with marked improvement until early in 1924, when headache began. Examination showed tumor of the skull. Roentgen-ray treatment completely removed this. In April, 1925, another tumor appeared in the skull; this improved on irradiation, but had an unfavorable outlook. Roentgen-ray examination showed the anterior end of the third rib completely destroyed for a distance of about 4 inches (10.1 cm.); the left side of the chest was filled with soft tumor.

Histologic examination revealed a cellular tumor, the cells with clear cytoplasm, in places diffuse, but mostly forming around vessels containing blood; perithelial arrangement was marked. The duration from onset was about four years.

CASE 14.—A boy, aged 17 years, with myeloma of the tibia (No. 173, registered by Dr. James Ewing), was admitted to Memorial Hospital, New York, Dec. 8, 1920, with a history of having had intermittent pain for one year and swelling for one month. Roentgen-ray examination showed the medullary canal somewhat expanded with periosteal proliferation. Excision of a piece for diagnosis had been made outside. The patient was treated with radium which was followed by improvement, with recurrence two years later. Amputation was done in December, 1923. In April, 1925, there was no sign of disease.

The duration from the onset was four and a half years; since amputation, one and a half years. Histologic examination revealed round and oval cells in lobules, surrounding vascular spaces. This was a rather diffuse angio type.

CASE 15.—A man, aged 22, with myeloma of the fibula (No. 400, registered by Dr. C. U. Collins, Peoria, Ill.), suffered the onset about Dec. 1, 1921, with swelling, fluctuating in size, and intermittent, not severe pain. Examination, Feb. 22, 1922, revealed a fusiform swelling of the leg. The roentgen-ray diagnosis was callus or probable sarcoma. Aug. 30, 1922, jelly-like tissue was excised. The pathologic diagnosis was mixed cell sarcoma. Sept. 1, 1923, there was recurrence. Radium treatments were given. Oct. 4, 1923, amputation was done. Roentgen-ray examination showed fracture, with swelling of the bone and some bone destruction.

Histologic examination revealed round, oval and some elongate cells in lobules. The cell had clear cytoplasm and a nucleus with scattered chromatin and was without an evident nucleolus—the type cell of this series. In places vessel-like spaces were formed; in places the cells were phagocytizing blood pigment. It was of angio-endothelial type. Oct. 25, 1924, the patient was well. The duration was three years after onset; one year after amputation.

CASE 16.—A man, aged 26, with myeloma of the humerus (No. 326, registered by Dr. H. W. Meyerding, Mayo Clinic), suffered an injury in March, 1920, which was followed by pain. Roentgen-ray examination showed a fracture and a tumor believed to be sarcoma. Most of the growth was excised, followed by treatment with radium, roentgen-ray and Coley's toxin. There was marked improvement but the wound did not heal. Aug. 22, 1923, amputation was done. Roentgen-ray and radium treatments were given. Roentgen-ray examination showed a large destructive tumor of the upper shaft with no new bone.

Histologic examination revealed an undifferentiated cell with scattered chromatin and no nucleoli. The cytoplasm formed a syncytium resembling an intercellular substance in places; other areas bore a resemblance to endothelioma as seen elsewhere. This was a rather diffuse angio type of Ewing's tumor. Feb. 28, 1925, the patient was well. The duration from onset was five years; from amputation, twenty months. (This case has been reported in full by Dr. H. H. Bowing.[22])

CASE 17.—A boy, aged 8 years, with tumor of the fibula (No. 267, registered by Dr. W. B. Coley), suffered trauma in the early part of 1920, followed by pain and swelling. Roentgen-ray examination showed considerable destruction of the shaft of the fibula with a mass infiltrating the soft parts. An operation was performed for exploration and later amputation. A large mass recurred in the iliac fossa on the same side, and there were metastases to the lungs. He had been treated with radium and Coley's toxin. A single large dose of roentgen rays was given, and all swelling disappeared.

Histologic examination showed a diffuse cellular tumor resembling Ewing's tumor. It was called diffuse endothelioma by Ewing. The patient was well in April, 1925, four years after onset, and about fifteen months after the last treatment.

CASE 18.—A girl, aged 12 years, with myeloma of the humerus (No. 83, registered by Dr. C. C. Simmons, Boston), had an obscure early history. She entered the hospital with a tumor of the humerus which after roentgen-ray examination was diagnosed as osteomyelitis and fracture. Incision and amputation were performed. The roentgen ray showed a destructive process in the shaft.

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22. Bowing, H. H.: S. Clin. N. A. 4:495 (Dec.) 1924.

Histologic examination revealed an undifferentiated cell with clear cytoplasm and scattered chromatin forming spaces and lining spaces, some of the spaces being entirely filled with tumor cells. There was uniform agreement that this was an angio-endothelioma. The patient was well four years after onset.

CASE 19.—No. 284 reviewed in text.

CASE 20.—*Living, duration under three years, and uncertain.* A boy, aged 7 years, with myeloma of the scapula (No. 515, registered by Dr. H. E. Isaacs, New York), March 14, 1923, struck the scapula against a bed. There was swelling but no pain, and this did not increase in the ensuing two weeks. The roentgen-ray diagnosis was tumor. Resection of the scapula with most of the muscles was performed, March 28, 1923. Roentgen-ray treatments were given, followed by recovery. The roentgenogram showed a tumor absorbing the bone, with no new bone formation.

Histologic examination revealed the type cell glued together by cytoplasmic substance, forming vessels. One vessel was nearly full of tumor cells. The patient was well in April, 1925. The duration from the time of operation was two years.

CASE 21.—A boy, aged 15, with myeloma of the clavicle (No. 547, registered by Dr. H. Flecker, Melbourne, Australia), in May, 1922, had pain in the right arm. In February, 1923, there was swelling. He had previously been treated for rheumatism. In June, 1923, sarcoma was diagnosed, and the clavicle (right) was excised. Roentgen-ray treatment was given. In February, 1924, there was swelling and pain of the upper right ulna. Roentgen-ray examination showed a metastatic tumor. Roentgen-ray treatment caused disappearance. In October, 1924, the patient was well.

Histologic examination revealed polyhedral cells with clear cytoplasm and scattered chromatin in the nuclei. The cells formed a reticulum. There was no intercellular substance. The duration from onset was two years, five months; from the last treatment, six months.

CASE 22.—A boy, aged 9 years, with myeloma of the humerus (No. 561, registered by Dr. Allen Graham, Lakeside Hospital, Cleveland), suffered the onset two years before examination, with intermittent pain and swelling. The pathologic diagnosis was sarcoma. Roentgen-ray treatment was given with improvement. Roentgen-ray examination showed a soft tumor destroying and invading the shaft.

Histologic examination revealed a diffuse endothelial myeloma. The patient was well two months after the treatment began. The duration was more than two years from the onset.

CASE 23.—A man, aged 20, with myeloma of the humerus (No. 618, registered by Roosevelt Hospital, New York), had two pathologic fractures, and had received a roentgen-ray diagnosis of sarcoma. Exploration and amputation were done. Roentgen-ray examination showed a very large, soft tumor of the shaft with bone laid down parallel with it.

Histologic examination revealed round cell tumor in diffuse sheets and lobules. W. C. Clarke considered it an "osteogenic sarcoma, Ewing's type." The patient was well six months after amputation. The duration from the onset was two and a half years.

CASE 24.—A female, age not given, had myeloma of the humerus (No. 629, registered by Dr. C. C. Simmons, Boston). In June, 1923, a swelling began, varying but increasing in size. Examination showed an oval tumor attached to and apparently originating from the bone. Roentgen-ray examination showed

tumor destroying the bone with no new bone formation. A piece was excised for diagnosis. Dr. J. H. Wright's diagnosis was: "It is not incompatible with an endothelioma or Ewing tumor." Radium treatment was given. The patient was under treatment in March, 1925, the growth having diminished considerably in size.

Histologic examination revealed round cells in diffuse masses, hyperchromatic nuclei. The picture was that of Ewing's diffuse myeloma. The duration to date has been nearly two years after onset.

CASE 25.—A boy, aged 11, with myeloma of the tibia (No. 339, registered by Dr. F. A. Besley, Cook County Hospital, Chicago), had received the examining room diagnosis of osteomyelitis. In December, 1922, the pain and swelling began; these grew rapidly. The roentgen-ray diagnosis was probably sarcoma. A piece was excised for diagnosis, which was round cell sarcoma. Coley's toxin was given, and roentgen-ray treatment each week for several months. The tumor markedly decreased in size. Treatment was begun in May, 1923; in November, the patient was getting well. Roentgen-ray examination showed a rather one-sided growth along the shaft of the tibia, affecting the periosteum and cortex, but also the medulla. There was no new bone.

Histologic examination revealed round cells, pale polyhedral cells with clear cytoplasm in lobules. No intercellular substance was formed by the tumor cells. This was a diffuse type showing no angiomatous characteristics. The duration from the onset was one year. No recent note has been made of the case.

CASE 26.—A girl, aged 8 years, with myeloma of the sacral vertebrae (No. 554, registered by Dr. J. E. Thompson, Galveston, Texas), suffered the onset in June, 1924, with swelling in the back and rheumatic pain in the left knee. Later there also was pain in the left foot, with a limp and foot drag. The roentgen-ray diagnosis was possible inflammation. Partial excision was done in July, 1924, followed by roentgen-ray treatment. In March, 1925, there were metastases to the skull, femur and lungs. Acute febrile attacks marked the development of the metastases. In April, 1925, the patient was improving under roentgen-ray treatment.

Histologic examination revealed endothelial myeloma. The outcome is uncertain. The duration to date has been eleven months.

CASE 27.—A boy, aged 10 years, with myeloma of the fibula (No. 418, registered by Dr. J. C. Bloodgood), had a history of injury to the leg two months before a swelling was noticed. There was no pain. The onset was about October, 1923. The roentgen-ray diagnosis was periosteal sarcoma. A piece was excised for diagnosis. Dr. Bloodgood's diagnosis was small round cell sarcoma—Ewing's endothelial myeloma. Amputation was performed by Dr. O. L. Miller, Gastonia, N. C. Dr. Bloodgood mentions that from the roentgen-ray examination and the gross appearance he diagnosed the sclerosing type of periosteal sarcoma with new bone formation. The roentgen-ray showed a fusiform tumor expanding the shaft with new bone formation, and with radiating spicules.

Histologic examination revealed that the growth could not be classed other than Ewing's tumor; the cells and the arrangement were typical; in one section an area resembled fibrosarcoma. This was a borderline case. Jan. 7, 1924, the patient was well.

CASE 28.—A male, no age given, had myeloma of the tibia (No. 292, registered by Dr. J. C. Bloodgood). Dr. J. C. Bloodgood received the tissue and roentgenograms from Dr. J. A. Brooke of Philadelphia without a history. Amputation was refused and roentgen-ray treatment was instituted. A piece was

excised for diagnosis about April, 1923. In October, 1924, there was a suggestion of recurrence. Dr. Bloodgood's diagnosis on the roentgenogram and an inadequate section was periosteal sarcoma; later, with better sections, there was a question of Ewing's endothelial myeloma. Roentgen-ray examination showed a tumor of the shaft characteristic of Ewing's tumor.

Histologic examination revealed a callus with much new bone formation; among and between the bone spicules were masses of cells resembling that found in Ewing's tumor, except that the nucleoli were somewhat more prominent.

CASE 29.—*Dead, duration from onset, three years.* A boy, aged 14 years, with myeloma of the os calcis (No. 258, registered by Dr. J. E. Thompson, Galveston, Texas), had had a progressive swelling which began in December, 1913. Amputation was done for sarcoma. The patient recovered completely, but died in the spring of 1922, following an operation for gallbladder disease. At operation, large retroperitoneal glands were seen. No roentgenograms were made.

Histologic examination revealed round cells forming vascular spaces resembling hemangio-endothelioma as seen elsewhere. In places the cells were in rows and in masses in lobules. The tumor was called osteogenic sarcoma by Wright, Hartwell, Stout and Case; a question of endothelioblastoma was raised by Mallory; endothelioma was the diagnosis of J. R. Paul and Christianson; Ewing's tumor of McFarland and Codman, and probable endothelioma of Ewing. In reviewing this with the others, there is no question but what it is a good example of the angio-endothelial type of bone tumor. The duration was more than eight years after amputation.

CASE 30.—A boy, aged 14 years, with myeloma of the fibula (No. 126, registered by Dr. P. P. Swett, Hartford, Conn.), had suffered trauma about October, 1919, with a slowly progressing swelling noted shortly after. When seen in October, 1921, the entire calf of the leg was enormously enlarged; the superficial veins were dilated; the inguinal nodes were large. The roentgen-ray diagnosis was sarcoma. October 31, most of the tumor and the inguinal glands were excised. The pathologic report was round cell sarcoma. Amputation was performed, Nov. 12, 1921. Radium was applied to the inguinal region, followed by recovery. In May, 1923, the patient was well. Roentgen-ray examination showed a large tumor involving most of the shaft of the fibula, and infiltrating the soft parts; there was no new bone.

Histologic examination revealed considerable inflammatory bone; there were round cells in masses and sheets between spicules of bone; one section showed true perithelial arrangement of cells. The patient died in November, 1924, of lung metastases. The duration from the onset was five years; from operation, four years.

CASE 31.—A girl, aged 14 years, with myeloma of the radius (No. 352, registered by Dr. James Ewing), in November, 1918, while pulling, felt a crackling sensation in the arm; the arm then began to swell and pain. The pain ceased; then became intermittent for the next year. The patient was treated with Coley's toxin and radium with marked improvement. Oct. 30, 1920, a specimen was excised. Later there were metastases to the skull, and the girl died, Dec. 31, 1921. Two roentgenograms of the tumor are shown in Ewing's "Neoplastic Diseases."[23] They are typical of the tumor, and show it before and after radium treatment.

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23. Ewing (Footnote 2, pp. 327, 328; Figs. 118, 119).

Histologic examination revealed a round cell tumor without intercellular substance, the cells seeming to join to form a cytoplasmic syncytium. The diagnosis was diffuse myeloma of the reticular type. The duration from the onset was three years.

CASE 32.—A boy, aged 6 years, with myeloma of the lower tibia (No. 538, registered by Dr. H. E. Ashbury, Baltimore), suffered the onset in December, 1919, with pain and swelling. There was local heat and a temperature of 102 degrees F. The roentgen-ray diagnosis several times was osteomyelitis. There were five operations, drainage and curettements, with four pathologic diagnoses of chronic inflammation. Finally tumors were found in the skull. Dr. Ashbury said: "Following metastases in the skull, June 15, 1922, the tumor in the tibia grew rapidly. The child required opiates continually for the relief of pain. The parents refused amputation. The child died two months later, in August, 1922. There was no necropsy." The roentgenograms at first showed a roughening of the periosteum resembling a periostitis; later, a diffuse tumor of the shaft expanding and eroding the cortex, but not forming new bone.

Histologic examination of one section revealed that it consisted of granulation tissue; of another, that it was a diffuse, very cellular tumor with cells similar to those in Ewing's tumor, in places tending to form vascular spaces. The duration from onset was nearly three years.

CASE 33.—A boy, aged 11 years, with myeloma of the scapula (No. 366, registered by Memorial Hospital Clinic), suffered the onset about the early part of 1920; there was pain and limitation of motion. He was treated with radium by Dr. J. C. Bloodgood at Baltimore; this controlled the pain and improved the motion. He became worse in the spring of 1922, and went to Germany for treatment, but came back in September, 1922, unrelieved. At Memorial Hospital, the tumor was excised with the head of the humerus (September, 1922). There were metastases in the left inferior maxilla, in the right tibia and in the lumbar spine. The left femur was treated with the roentgen-ray, which helped temporarily. The pathologic diagnosis by Dr. Ewing of the tissue removed was endothelial myeloma. The patient died sometime in 1923. The roentgen-ray report mentions metastasis to the lungs; no roentgenograms were made. The duration was about three years.

Histologic examination revealed that the tumor was a good example of the somewhat lacy reticulated type, forming vascular spaces partly filled with tumor cells. The cells had clear cytoplasm, and round to oval nuclei with deeply staining, but diffuse chromatin.[24]

CASE 34.—*Dead, duration less than three years.*[25] A girl, aged 3 years, with myeloma of the femur (No. 430, registered by Children's Hospital, Boston), fell in May, 1923. A week later she suffered pain, with a temperature of 104 F. The roentgenographic diagnosis was made and an operation for osteomyelitis performed outside. At the hospital the pain was intermittent, the roentgen-ray diagnosis being that it was "not characteristic of new growth." Exploration was done. The diagnosis of Dr. Wolbach was Ewing's tumor. The patient left the hospital without further treatment, and died, Sept. 18, 1924, with a massive growth and emaciation. Roentgen-ray examination showed a large destructive tumor of the shaft of the humerus.

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24. Ewing (Footnote 2, p. 329; Fig. 120 is a photomicrograph of this tumor).
25. The average duration from onset in this group is about thirteen months.

Histologic examination revealed a diffusely cellular tumor invading the soft parts, the type cell seen in Ewing's tumor, with a few cells resembling plasma cells. The duration was sixteen months.

CASE 35.—A man, aged 48, with myeloma of the tibia, fibula and bones of the tarsus (No. 534, registered by Dr. W. A. Evans, Detroit), had enlarged inguinal glands when first seen. The onset was in July, 1923, with inflammation of the skin of the leg. Later, there were two fractures. Amputation was done, Dec. 22, 1923. The inguinal glands were given four roentgen-ray treatments, the patient refusing more. He died in July, 1924. Roentgen-ray examination showed a diffuse infiltration of the entire tibia, with mottling of the fibula and astragalus and other bones of the tarsus.

Histologic examination revealed a diffuse cellular tumor composed of small round cells resembling those seen in Ewing's tumor. The section was not good, and it was not definitely diagnosed histologically, but it conformed clinically with this type. The duration was one year from onset.

CASE 36.—A woman, aged 24, with myeloma of the clavicle (No. 162, registered by Dr. C. C. Simmons, for the Collis P. Huntington Memorial Hospital, Boston), about November, 1921, noticed lameness in the left arm, with some pain. This disappeared but there were periods of pain which would last for a few days then disappear for a week or two. The swelling appeared about six weeks later. The first diagnosis (outside) was periostitis. Dr. Simmons' diagnosis was sarcoma. The clavicle was excised. Radium treatment was given. The pathologic report of Dr. Wright was "a cell-rich sarcoma; the cells were small, not characteristic, with scanty cytoplasm, and showed no tendency to differentiate into bone or cartilage cells." Roentgen-ray examination showed a destructive tumor at the outer end of the clavicle. The patient died, Dec. 1, 1922, with masses in the spine, lungs, liver and retroperitoneal glands. The duration was about one year.

CASE 37.—A boy, aged 3 years, with myeloma of the femur (No. 215, registered by Dr. J. W. White, Massachusetts General Hospital, Boston), caught his foot in a fence a year before the history was taken. Three months later, he had pain. Nine months later, a roentgen-ray diagnosis of osteomyelitis was made. A later roentgen-ray diagnosis was sarcoma or osteomyelitis. Exploration and drainage were done. H. F. Hartwell's diagnosis was osteogenic sarcoma. Sixteen roentgen-ray treatments were given with temporary relief. The patient died a few months after discharge. Roentgen-ray examination showed swelling of the shaft of the femur with bone destruction; there were lines of dense tissue running through without any definite arrangement.

Histologic examination showed mostly chronic inflammatory tissue; on the edge of one slide was tissue like that of Ewing's tumor. This was diagnosed inflammation by Mallory, Wolbach, MacCallum, MacCarty and Broders; osteogenic sarcoma by Hartwell, Wright, Graham and McFarland; malignant tumor, possibly osteogenic (from roentgen-ray examination) by Ewing, and possible Ewing's tumor by Robinson. The registrar and I think that it cannot be classified as other than Ewing's tumor. The duration was about two years after onset. The patient died of lung metastases.

CASE 38.—A man, aged 30, with myeloma of the ulna (No. 340, registered by Dr. J. C. Bloodgood), suffered trauma about August, 1921; this was followed by swelling and pain, which subsided. Trauma a second time was followed by swelling and pain. The roentgen-ray diagnosis was osteitis. Dr. Bloodgood's roentgen-ray diagnosis was periosteal or soft parts tumor. An incision was

made, and Dec. 13, 1922, amputation was done by Dr. C. H. Harris, Fort Worth, Texas. The pathologic diagnosis was round cell sarcoma. Roentgenograms were not included.

Histologic examination revealed a cellular tumor, tending to be perithelial in arrangement; no intercellular substance. Angio-endothelioma was suggested. The patient died, May 18, 1923, with metastases to the lungs. The duration from onset was one year, nine months; from operation, six months.

CASE 39.—A man, aged 20, with myeloma of the ilium (No. 463, registered by Maj. J. F. Coupal, Washington), had been kicked in the right knee by a horse in May, 1921. Shortly after there was pain in the knee and the hip, which was diagnosed rheumatic arthritis on two occasions. Later, an operation was performed for suppurative arthritis of the hip, but no disease was found. Roentgen-ray examinations were at first negative; later they showed sarcoma of the ilium. The patient died about a year after the onset with metastases to the skull, lungs, spleen and mesenteric nodes. Roentgen-ray examination showed a large irregular area of bone destruction in the ilium, with some bone production around the edge.

Histologic examination revealed medium size cells in the lobules, the cell being similar to that in Ewing's tumor; in the lung and spleen these cells were surrounding and forming spaces, some spaces being partly filled with the cells. It was a good angio-endothelioma type.

CASE 40.—A boy, aged 9 years, with myeloma of the os calcis (No. 385, registered by Dr. J. E. Thompson, Galveston, Texas), which began in October, 1922, with sharp pain and fever. He had several attacks, with pain in the other bones. The roentgen-ray diagnosis was osteomyelitis or tumor. This was excised and curetted, Sept. 13, 1923. Five roentgen-ray and seven radium treatments were given with slight improvement. Dr. V. H. Keiller's report on tissue was osteogenic sarcoma. The roentgenograms showed bone absorption with a tumor breaking through the periosteum, and with some new bone in no definite arrangement.

Histologic examination revealed purple staining cells closely packed in places in rows with very little stroma. The tumor was lobulated, invading the soft tissues. The cell type was similar to that seen in endothelioma, with an occasional plasma cell and undifferentiated marrow cells. The patient died, May 15, 1924, with metastases to many long bones, the ilia, the skull, the lungs and the kidney. The duration from onset was one year, seven months; from operation, eight months. The final diagnosis was diffuse myeloma.

CASE 41.—A man, aged 25, with myeloma of the ilium (No. 444, registered by Presbyterian Hospital, New York), sprained his back in February, 1915. The pain began in August, 1915; the swelling in October. He lost 20 pounds (9 kg.) in weight. Roentgen-ray examination showed bone destruction. A diagnostic incision was made in February, 1916. He was treated with the roentgen ray, radium and Coley's toxin. He died in September, 1917, with lung metastases.

The histologic report by Wright, Hartwell, Graham, Callender, Coupal and Ewing was endothelioma. The duration was two years after onset; one year, seven months after beginning treatment.

CASE 42.—A boy, aged 8 years, with myeloma of the ulna (No. 350, registered by Dr. J. Ewing), suffered the onset shortly after a fall, with gradual enlargement but no pain. The roentgen-ray diagnosis was periosteal sarcoma or endothelioma. A section was removed. There was marked recession under radium

treatment and Coley's toxin. Enlargement followed, and amputation was done. Notes from the roentgen-ray reports were: 1. At first, there was a diffuse lytic process in the shaft. 2. Under radium treatment there was an increase in the density of the cortex. 3. Except for slight thickening of the cortex, there was no disease. 4. There was definite evidence of new bone formation in the periosteum. It was laid down at right angles to the shaft as in periosteal sarcoma. 5. There was more bone production.

Histologic examination revealed angio-endothelioma. The patient died eighteen months after onset.[26]

CASE 43.—A boy, aged 13 years, with myeloma of the tibia (No. 161, registered by Dr. J. W. White for the Massachusetts General Hospital, Boston), suffered the onset, Feb. 4, 1921, three days after a fall on the ice. There was pain, local heat and tenderness. He recovered, but one week later felt pain, lasting for four days. Still later, there was pain and a tumor appeared. The roentgen-ray diagnosis was sarcoma; the first interpretation, however, was probably osteomyelitis. Amputation was done, March 30, 1921. One roentgen-ray treatment was given. Roentgen-ray examination showed a partial destruction of the cortex, with periosteal fragmentation.

Histologic examination revealed round cells arising in a reticulated myxomatoid matrix, forming and lining spaces. The cells had clear cytoplasm and densely staining nuclei. There was much new bone formation, some of which was hard to distinguish from tumor bone. There was considerable disagreement on this tumor. Ewing says, "I am much interested in this case, which I think shows the very beginning of endothelioma of bone." Mallory says, "Not a tumor;" Wolbach says, "Repair in bone," and Bloodgood diagnosed it as "not malignant." Wright and Hartwell regarded it as a tumor, possibly metastatic, but later thought it to be osteogenic. The patient died of "sarcomatosis," March 20, 1922. The duration had been one year.

CASE 44.—A girl, aged 16, with myeloma of the eleventh rib (No. 99, registered by Dr. J. C. Bloodgood, Baltimore, and Dr. C. S. Hoffman, Keyser, W. Va.), fell on the side three years before the tumor of the rib became noticeable. Excision was done, April 13, 1920, with recurrence in the other ribs. This was followed by excision and cautery, June 16, 1920. No roentgenograms were made.

Histologic examination revealed round cells in sheets and in lobules, some forming pseudorosettes and some gathering around pale pink liquid. A few plasma cells and bone marrow cells were present. The tumor was of the diffuse myeloma type. The patient died in October, 1920. The duration from onset was unknown; from the first operation, it was six months.

CASE 45.—A man, aged 24, with myeloma of the ilium (No. 449, registered by Presbyterian Hospital, New York), entered the hospital with a history of progressive swelling and pain. An incision was made for diagnosis, the roentgen-ray examination having shown a tumor resembling sarcoma. The patient died five months later, ten months after onset. The roentgen-ray report was "diminished density and roughening of the cortex."

Histologic examination revealed a very cellular tumor with many mitotic figures, the cells round, deeply staining and forming imperfect blood spaces. There were numerous plasma cells, but no intercellular substance. The history

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26. Ewing (Footnote 2; Figure 117 is a reproduction of the roentgenogram of this patient).

was imperfect, but the histology was definite. The patient died with numerous metastases. The duration was about ten months.

CASE 46.—A woman, aged 54, with myeloma of the ischium (No. 359, registered by Memorial Hospital Clinic), suffered the onset about March, 1922, with a dull pain radiating down the right leg. The roentgen-ray diagnosis was endothelioma with metastases to the lung. Previous to entry she had had a local removal. Roentgen-ray treatment was given with marked temporary improvement. The patient died, Aug. 18, 1922.

Histologic examination revealed cells in masses and rows, in lobules. The section was too poor for accurate diagnosis. Dr. Ewing saw the original sections and diagnosed endothelioma. The roentgenogram was of a destructive process involving the right ischium. Only a faint outline of the cortex was seen. There was no new bone formation. The duration from onset was about six months. (The early history of this case was very indefinite.)

CASE 47.—A boy, aged 13 years, with myeloma of the fibula (No. 108, registered by Dr. J. C. Bloodgood), suffered the onset with pain and swelling in November, 1920, two months after an injury. Amputation was done in December, 1920, followed by temporary improvement. There were metastases to the skull in March, 1921. The patient died, Sept. 21, 1921, from metastases to the skull, lungs and ribs.

The duration was eleven months after onset; eight months after amputation. The roentgen-ray diagnosis was periosteal sarcoma. The roentgenograms showed a diffuse swelling of the shaft of the fibula, with radiating bone spicules on one side. It was not definitely an endothelioma. Histologic examination revealed round cells infiltrating the muscle and fascia. The section was poor, and was not definitely diagnosed Ewing's tumor.

CASE 48.—A boy, aged 14 years, with myeloma of the femur (No. 120, registered by Dr. J. C. Bloodgood), suffered the onset about October, 1920, with pain followed by swelling. He was thought to be rheumatic. The roentgen-ray diagnosis was periosteal sarcoma. Amputation was done, June 18, 1921. There was recurrence in the stump, the back, the skull and the lungs. The patient died in June, 1921. Roentgen-ray examination showed a growth within the bone, the periosteum roughened and some new bone laid down parallel with the shaft; the tumor was at the lower end of the bone.

Histologic examination revealed mostly a bony callus, which was not tumor bone, cells growing in and apparently from the reticulum, and masses of cells without intercellular substance. The duration from onset was eight months.

CASE 49.—A man, aged 25, with myeloma of the humerus (No. 164, registered by Dr. H. H. Hartung, Boston), suffered trauma in August, 1921, which was followed by swelling and pain. He came into the hospital for acute intestinal obstruction, for which an operation was done. During his stay a periosteal sarcoma of the humerus was diagnosed by roentgen ray. A gland in the axilla was removed. He made a poor recovery from an abdominal operation. He died, Feb. 16, 1922, from an unknown cause, having left the hospital. Histologic examination revealed cells with pink cytoplasm and definite nucleoli, resembling plasma cells; these were in rows and masses, and in lobules. No final diagnosis was made. Ewing calls it diffuse endothelioma or myeloma; Mallory and Wolbach, undifferentiated sarcoma. The duration from the onset was about six months.

CASE 50.—A man, aged 40, with myeloma of the vertebrae, ribs and skull (No. 485, registered by Dr. E. J. Mullaly, from the Royal Victoria Hospital, Montreal), said that the tumor began with pain in the spine, following a jolt

when motoring. Later, he had pain in the chest and difficulty in walking. No Bence-Jones protein was found. Leukocytes totaled 27,000-15,000. There were small hemorrrhages from the hypodermic needle punctures and oozing from the gums. The clinical diagnosis was multiple myeloma. Roentgen-ray examination showed mottling of the vertebrae, some of which were collapsed. The pathologic report was a positive oxidase reaction in the tumor cells.

Histologic examination revealed round cells, some with no cytoplasm; others with a small amount of deeply staining cytoplasm, and undifferentiated round cells resembling myeloblasts. The reticulum was not collagenous, and there was a capillary stroma. The patient died with metastases to the lungs, liver, spleen and kidneys. The duration was less than five months.

CASE 51.—A man, aged 34, with myeloma of the third metatarsal (No. 298, registered by Dr. L. R. Chaput, Haverhill, Mass.), suffered trauma with fracture of the second metatarsal, March 16, 1923. This healed, but pain and swelling continued. May 7, 1923, the second metatarsal healed, but a destructive process involved the third. The roentgen-ray diagnosis was questionable osteomyelitis. This was excised and radium treatment was given. Aug. 4, 1923, amputation was done. Roentgen-ray examination showed a tumor destroying the bone, with no new bone formation.

Histologic examination revealed round cells in sheets and rows, with elongate cells in whorls forming indefinite vascular spaces. It was of a diffuse type. The patient died, August 18. The duration was not longer than five months after onset; two weeks after amputation. There were brain (skull?) metastases.

CASE 52.—A girl, aged 13 years, with myeloma of the femur (No. 266, registered by Dr. G. A. Rice, Holden, Mass.), had an indefinite history of trauma some months before onset, which was in September, 1922. There was continued swelling of the thigh, with twinges of pain below it. The roentgen-ray diagnosis stated that there was a question of sarcoma, osteomyelitis and syphilis. Exploration was done, Dec. 30, 1922, followed by roentgen-ray and radium treatment. Metastases in the skull were later reduced by radium, but the patient died, May 12, 1923. Roentgen-ray examination showed expansion of the cortex by a tumor mass destroying the bone. Some new bone was produced, laid down parallel with the shaft.

Histologic examination revealed round, oval, sometimes elongate cells in sheets and lobules, with dense nuclei, some in whorls, the greatest number surrounding cavities filled with liquid or blood. This was considered a true perithelioma. The duration from onset was eight months; from the beginning of treatment, five months.

CASE 53.—A man, aged 25, with myeloma of the fibula (Massachusetts General Hospital, Case 1), in October, 1915, turned the left ankle. This was followed by pain and swelling, which disappeared. In January, 1916, he received an injury to the same ankle. Three days later, there was increasing pain and swelling. The roentgen-ray diagnosis (outside) was osteomyelitis. Curettement was done, with removal of pus, after which the patient was better. In June, 1916, there was pain and swelling, the pain being intermittent. At the Massachusetts General Hospital, a tentative roentgen-ray and clinical diagnosis of giant cell tumor was made. In October, 1916, the fibula was resected. The patient died one and a half years later of recurrence and lung metastases (see text for pathologic description).

CASE 54.—A boy, aged 13 years, with myeloma of the tibia (Massachusetts General Hospital, Case 2), in the spring of 1903 had lameness, which began in

the right leg. In the fall, swelling began. There was some pain day and night. He walked with a crutch for some time, three or four months. The leg was lanced twice outside, but only blood was obtained. At the Massachusetts General Hospital a fusiform swelling of the leg was found; the skin was tense, shiny and purplish, with large vessels. There were slight tenderness, with no fluctuation, and a granulating surface from the previous operation. Amputation was done, Jan. 15, 1904, by Dr. Warren.

Dr. W. W. Whitney's description was: "In the lower leg was a spindle-shaped swelling extending from just above the ankle to just beneath the head of the tibia, about 6-8 cm. in one diameter by 10 in the other. Upon section it was found to be a new growth, extremely soft, almost diffluent, which had entirely destroyed the fibula for a distance of 5 or 6 cm. Below this the bone was thickened to about double its normal size for a distance of 1 or 2 cm. The tumor mass was lobulated and quite sharply marked off from the surrounding tissue. Microscopic examination showed it to be composed of very small round cells with very little intercellular substance divided into lobules by bands of connective tissue."

Reexamination of the original slides showed this to be a typical Ewing's tumor. The tumor was preserved in the Warren Anatomical Museum of the Harvard Medical School, from which it was obtained for study and roentgenograms. These show a typical Ewing's tumor (Fig. 14). The patient died in May, 1904, with symptoms indicative of metastases to the other leg, the left arm and the skull. The duration was about a year from onset; four months after amputation.

EXPERIMENTAL HYDRONEPHROSIS

THE EFFECT OF LIGATURE OF ONE BRANCH OF THE RENAL ARTERY ON ITS RATE OF DEVELOPMENT *

IV. Simultaneous Ligation of the Posterior Branch of the Renal Artery and the Ureter on the Same Side

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The effect on the kidney of the ligation of one branch of the renal artery has been the object of much investigation, concerned chiefly with the question of an arterial collateral circulation as shown by the pathologic changes, particularly relative to regeneration in the infarcted area,[1] and rarely with the question of functional activity and restoration.[2] It is the purpose of this paper to present an experimental study in the rabbit of the effect of this procedure on the rate of development of hydronephrosis.

ANATOMIC CONSIDERATIONS

The arterial distribution of the kidney is divided almost equally into an anterior and a posterior division which are entirely devoid of anastomoses or intercommunications.[3] Each is an independent and an end system. In the majority of animals with one-lobed kidneys (dog, sheep, rat and cat), the posterior division is the larger and supplies a greater area of parenchyma than the anterior division, but in the rabbit the reverse is true, and the anterior division preponderates, as in man.[4] The relative distribution in the rabbit is illustrated in Figures 1 and 2, in which the anterior branch of the renal artery has been divided between ligatures. The roentgenogram after barium sulphate injection,

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* From the Department of Urology and Hooper Foundation for Medical Research, University of California Medical School.

* Part of scientific exhibit on pathogenesis of hydronephrosis presented at the Seventy-Fourth Annual Session of the American Medical Association, San Francisco, June, 1923.

1. McNider: J. M. Res. **24**:425-454, 1911. Thorel: Virchows Arch. f. path. Anat. **146**:297-330, 1896. Foa: Beitr. z. path. Anat. u. z. allg. Path., 1889, p. 277. J. Rose Bradford: Croonian Lecture, Lancet **168**:191, 1904.

2. Marshall, E. K., Jr., and Kolls, A. C.: Am. J. Physiol. **49**:335-338 (July) 1919.

3. Hyrtl: Topographische Anatomie, Vienna **1**:834, 1882.

4. Kelly and Burmann: Diseases of the Kidneys, Ureters and Bladder **1**:141. Morison: The Study of the Renal Circulation with Special Reference to Its Finer Distribution, to be published.

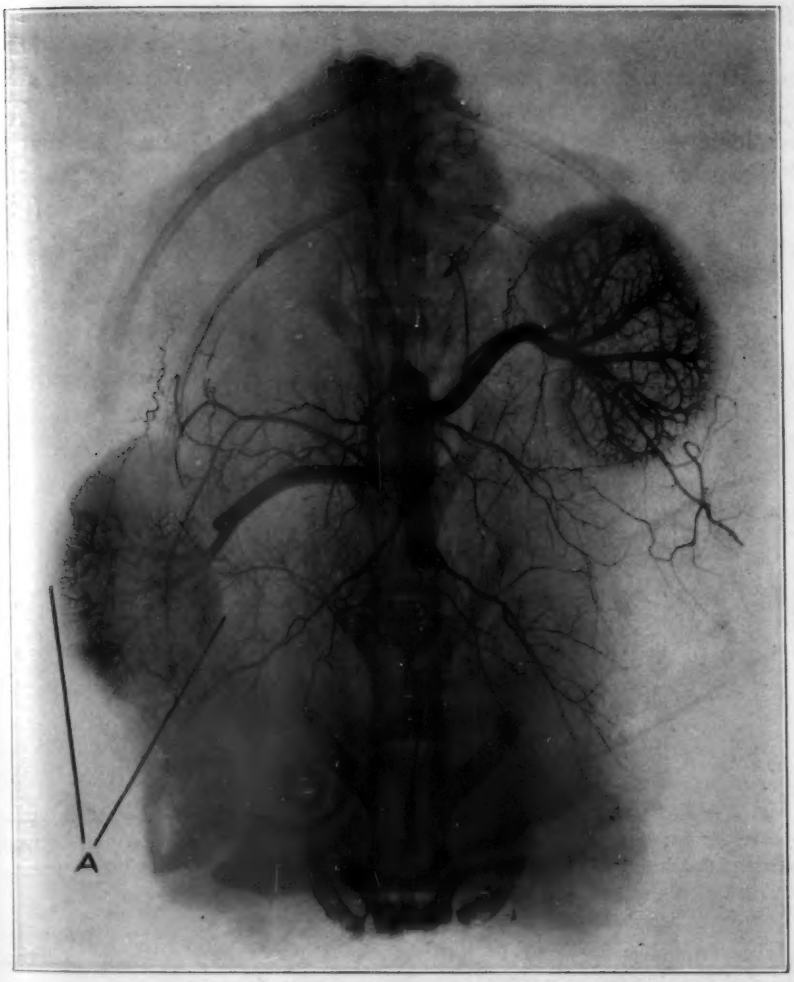

Fig. 1.—Roentgenographic appearance after arterial barium sulphate injection of kidneys of rabbits in situ; left side, anterior branch of renal artery divided between ligatures; injection demonstrates usual area of distribution of posterior branch, *A*.

from the aorta, demonstrates the smaller area of distribution of the posterior branch.

The renal artery is an end artery in the true sense of the word, and since there is no intrarenal communication between the two divisions, ligation of either one will result in complete infarction of the area of the kidney which that branch supplies. In the rabbit, anatomic studies demonstrate that the posterior branch of the renal artery supplies approximately from one third to one half of the kidney mass. The pathologic changes (illustrated in Figure 3, which shows the margin of the infarct after seven days) are those of anemic infarction and acute degenerative processes, followed by fibrosis and atrophy of the area involved.

Fig. 2.—Roentgenographic appearance of arterial barium sulphate injection of posterior branch of renal artery of rabbit; anterior branch divided between ligatures; the kidney has been cut sagitally to demonstrate the relative area of distribution of the anterior and posterior branches.

The functional changes that follow this procedure need further investigation. Marshall and Kolls [2] state that the urinary output is reduced to half that of the normal kidney, but Butler, in a study of secretory pressure and function in this laboratory, noted a reduction, but not to the degree that they claim to have found. The functional change is closely related to the problem of renal reserve, as well as to that of the relation of secretory pressure to function. In connection with the present problem, the effect on secretory pressure of ligation of one of their two main arterial branches is of importance. Reduction of function by half might signify reduction by half of secretory pressure,

Fig. 3.—Margin of infarct seven days after ligation of posterior branch of renal artery; lighter area to the right represents the infarct; degenerative changes are marked.

and such a reduction in back pressure might alone be expected to affect markedly the rate of development of hydronephrosis. A permanent reduction in back pressure, according to the general conception, would necessarily reduce the ordinary rate of development. A glance at Figure 4, compiled from Butler's protocols, shows that the renal reserve of half a kidney is capable of maintaining both function and secretory pressure to nearly the point of both before ligature of the posterior branch, and a slowing in the rate of development of

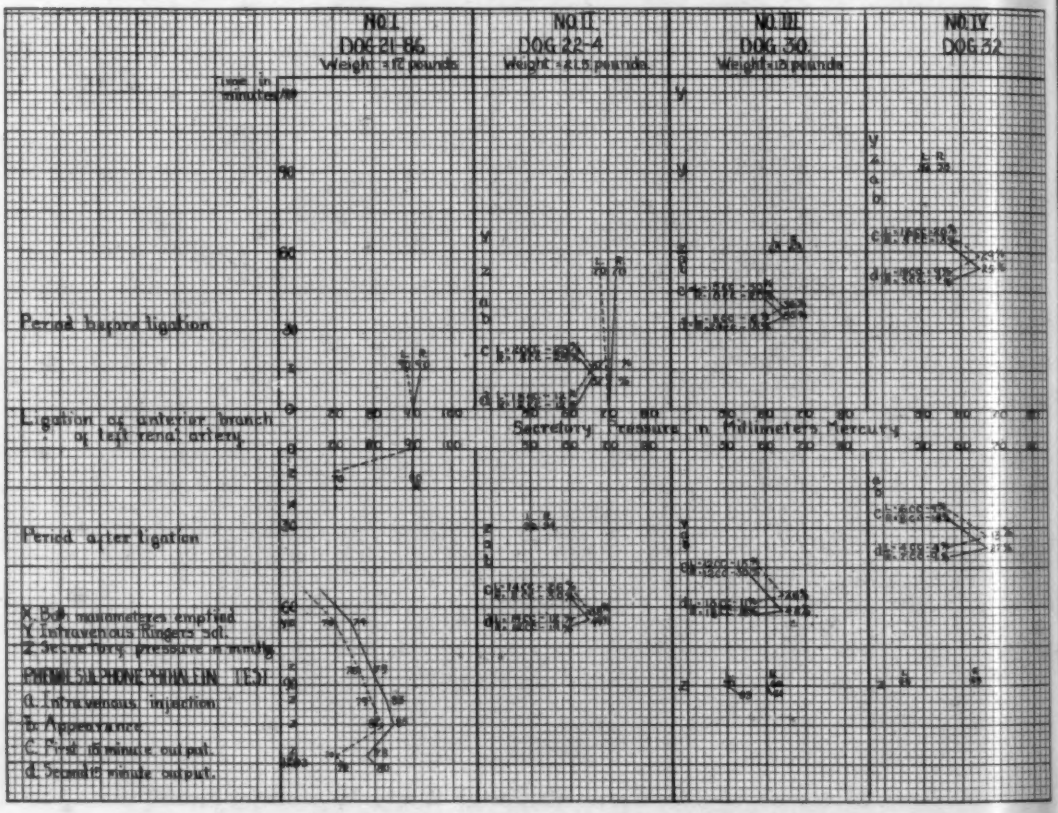

Fig. 4.—Effect of ligation of one branch of renal artery on secretory pressure. In only one of the four experiments was there as great as 30 per cent. difference in the secretory pressure of the two kidneys after ligation of the one branch of the renal artery of one kidney, and in three their difference was only from 15 to 20 per cent., instead of a 50 per cent. reduction, as ordinarily reported, and as might be expected after limitation of blood supply by one half. Unquestionably, there is not a 50 per cent. anatomic removal. The increased flow and vascular dilatation of the undisturbed half compensates for the loss by ligature, as is also shown by the behavior to phthalein excretion after ligature; only in Experiment 4 was there a 50 per cent. reduction of phthalein output, and in this experiment the greatest difference in secretory pressure occurred.

hydronephrosis can hardly be expected since the back pressure is so little reduced whereas the renal mass is diminished by almost one half. The significance of this condition is emphasized by comparison of the normal rate of complete renal destruction after ureteral ligation in the different species of different weights. Small kidneys undergo complete hydronephrotic atrophy in a much shorter time compared to large kidneys (Fig. 5).

The theoretical point worthy of emphasis at the outset is that ligature of one branch of the renal artery should hasten the rate of development of hydronephrosis provided back pressure is the essential factor of hydronephrotic atrophy, because the renal mass has been

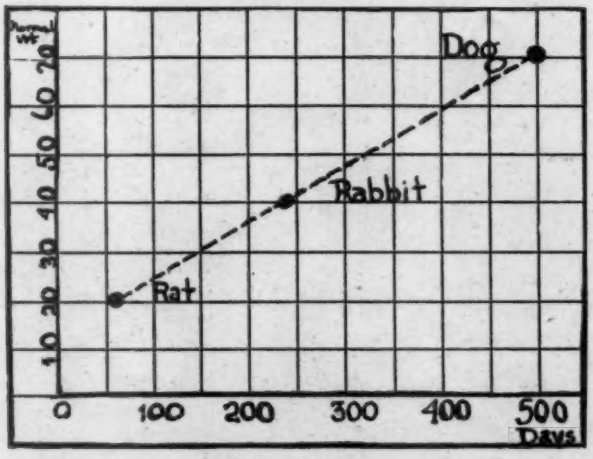

Fig. 5.—Stage of complete hydronephrotic atrophy in rat, rabbit and dog to demonstrate variation in rate in different animals; ordinate represents weight of normal kidney, abscissa number of days for complete hydronephrotic atrophy to occur.

reduced one half and back pressure little, if at all. In a previous paper,[5] an insight into the true significance of back pressure and anemia to hydronephrotic dilatation and atrophy was indicated by results following partial constriction of the renal artery which reduced both secretory pressure and function but hastened hydronephrotic atrophy, and this acceleration in rate of dilatation and atrophy was attributed to an increased anemia. The following results further emphasize this conclusion.

5. Hinman, Frank; and Hepler, A. B.: The Effect of Changes in Blood Pressure and Blood Flow on the Rate of Development of Hydronephrosis, III, Partial Compression of the Renal Artery, Arch. Surg., to be published.

Fig. 6.—Gross specimen in situ of fourteen day hydronephrosis of left kidney of rabbit with ligation of posterior branch of renal artery; anterior half of kidney embedded in large saccular dilatation of posterior half, which has been deprived of its blood supply.

EXPERIMENTAL DATA

Technic.—In twelve rabbits, the left kidney was exposed through a lumbar incision, and the ureter divided between ligatures 4 cm. from the ureteropelvic junction. The point of division of the renal artery into its anterior and posterior branches was found, and the posterior

Fig. 7.—Lower: sagittal section of sac in a fourteen day hydronephrosis with ligation of posterior branch of renal artery; opening, *A*, in middle of right half communicates with dilated pelvis of remaining parenchyma in anterior one third of sac; upper: simple hydronephrosis for the same period (Fig. 6).

branch divided between ligatures. In the first animals used, the posterior branch was simply ligated, but, at necropsy, when an arterial barium sulphate injection was made through the aorta, using 300 mm. of

Fig. 8.—Fourteen day hydronephrosis with ligation of posterior branch of renal artery; anterior portion of kidney whose blood supply was undisturbed split open to show dilatation of pelvis which has progressed to degree usually seen after fourteen days of ureteral obstruction. This pelvis communicates by the opening, *A*, seen in Figure 5, with the sac or diverticulum represented by the lighter portion behind, *B*.

mercury pressure, it was found that some of the barium passed this ligature. Since this would cause confusion in the interpretation of the roentgenograms, these animals were discarded, and, subsequently, the artery was divided between ligatures. When it was sectioned, the occlusion of the circulation was confirmed by the blanching of the kidney surface corresponding to the area of anemic infarction.

Findings.—The rabbits were killed seven, fourteen, twenty-one, twenty-eight, fifty-six and ninety days following operation. We had previously determined [6] the rate of the development of hydronephrosis with simple unilateral ureteral obstruction (Table 1). A comparison

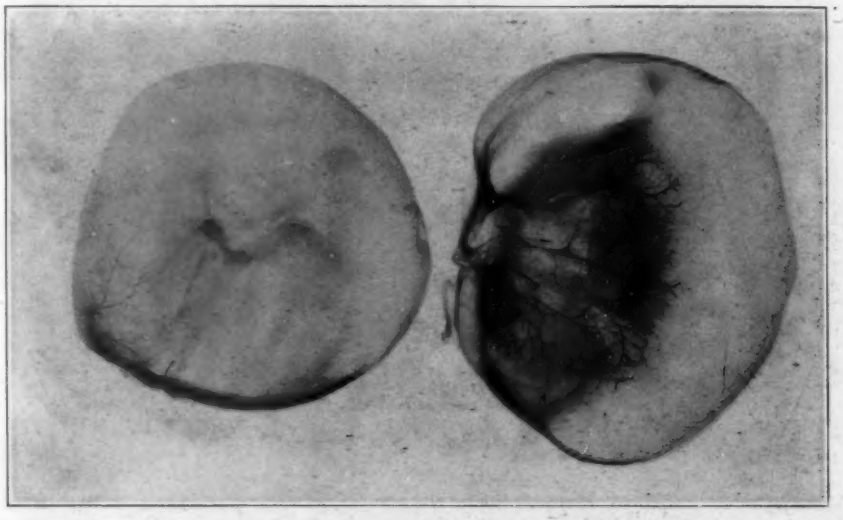

Fig. 9.—Roentgenographic appearance after arterial barium sulphate injection of a fourteen day hydronephrosis with ligation of posterior branch of renal artery of rabbit; kidney has been cut sagitally to demonstrate the absence of arterial injection in the sac, the injection representing the undisturbed anterior branch.

of these figures and the measurements given in Table 2 indicate the remarkable variation that takes place in the development of hydronephrosis when a branch of the renal artery is ligated, but these figures alone give no adequate idea of the actual conditions found.

The findings, after ligation of the ureter and the posterior branch of the renal artery, in twelve rabbits, may be summarized under four different types of changes.

6. Hinman, Frank; and Hepler, A. B.: The Effect of Changes in Blood Pressure and Blood Flow on the Rate of Development of Hydronephrosis, I, Splanchnotomy, Arch. Surg., to be published.

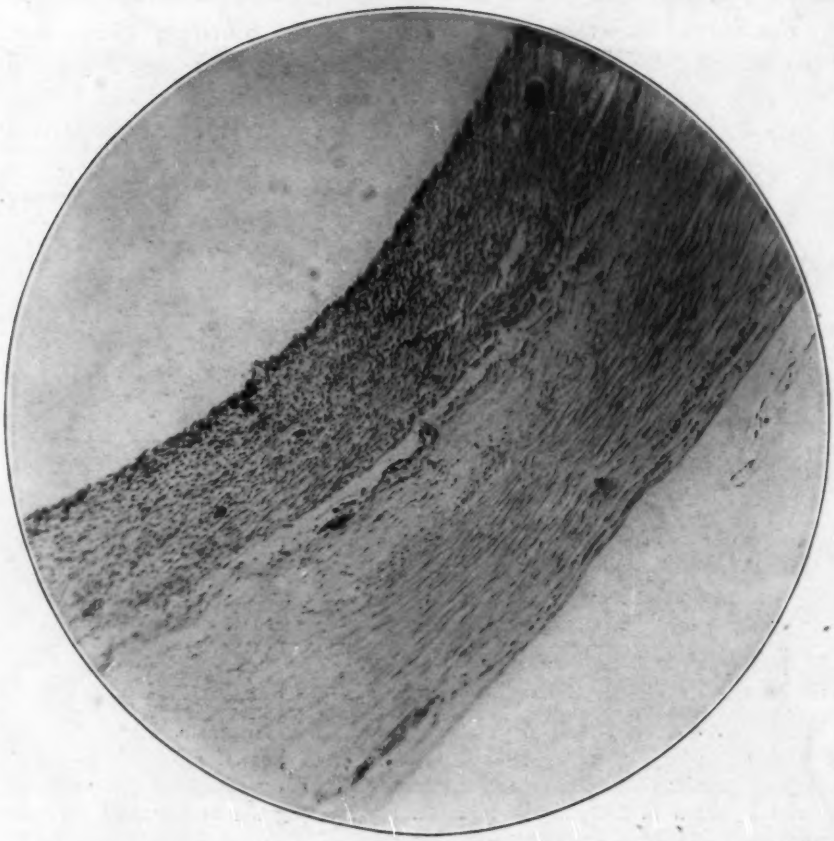

Fig. 10.—Sac or diverticulum that results in a fourteen day hydronephrosis when posterior branch of artery is ligated; remarkable acceleration in development of hydronephrotic atrophy brought about by an exaggerated degree of parenchymal degeneration (infarction); after fourteen days, atrophy and connective tissue substitution are greater than occur with 242 days of simple ureteral obstruction (Fig. 11).

1. The formation of a pelvic diverticulum. The infarcted area undergoes degeneration, but, under the influence of intrapelvic pressure plus anemic atrophy, dilates to an enormous degree so as to become an offshoot or diverticulum of the pelvis with which it communicates by a small opening. The anterior portion of the kidney undergoes hydronephrotic atrophy to the degree usually seen in simple hydronephrosis for the same periods of obstruction (seven rabbits).

There is very little difference noted for the seven day period, but the condition found in the fourteen day specimen is unique, and can

Fig. 11.—Two hundred forty-two day rabbit hydronephrosis (low power), showing thickened capsule, atrophic tubular elements and a few well preserved glomeruli.

best be appreciated by a study of the illustrations. The following notes were made at necropsy:

The left kidney was markedly enlarged, being 7.5 cm. long, 6 cm. deep, and 5.5 cm. wide. It consisted of a moderately thick walled sac, which presented on its anterior surface a thin shell of kidney parenchyma (Fig. 6).

The sac, which was not adherent to any surrounding structure, was covered with dilated veins and a few small arteries. It had a

capacity of 105 c.c., and was filled with a brownish, grumous material. On section, the wall was tough and fibrous. The inner surface of the sac presented anteriorly a fenestrum, 1 cm. in diameter (Fig. 7), which was surrounded by a grayish, pultaceous degenerated tissue, and which communicated with the dilated pelvis of the remaining kidney parenchyma (Fig. 8). This constituted about one third of the original kidney mass.

TABLE 1.—*Measurements of the Hydronephrotic Kidney in Rabbits After Total Ligation of the Left Ureter*

Duration. Days	Weight of Rabbit, Kg.	Measurements of Kidney			Pelvic Capacity, C.c.
		Length, Cm.	Depth, Cm.	Width, Cm.	
7	4	5.2 (0.1)*	3.5 (0.0)	3.3 (0.3)	4
14	2.72	4.3 (0.55)	3 (0.48)	2.8 (0.74)	6
21	4	6 (.09)	4.4 (0.4)	3.8 (0.76)	14
28	3.02	5 (1.13)	3.4 (0.38)	3.5 (1.21)	18
56	3	5.2 (1.36)	3.7 (0.7)	3.5 (1.22)	25
90	2.89	5.5 (1.8)	3.8 (0.91)	3.6 (1.41)	33

* The figures in parenthesis indicate the actual increase in size when the measurements are proportioned to the animal's weight, using as a normal standard a rabbit that weighed 2.5 kg. and whose left kidney was 3.2 cm. long, 2.5 cm. deep and 1.9 cm. wide.

TABLE 2.—*Measurements of the Hydronephrotic Kidney in Rabbits After Total Ligation of the Left Ureter and Ligation of the Posterior Division of the Renal Artery*

Duration. Days	Weight of Rabbit, Kg.	Measurements of Kidney			Pelvic Capacity, C.c.
		Length, Cm.	Depth, Cm.	Width, Cm.	
7	2.78	4 (0.43)*	2.5 (0.0)	2.7 (0.58)	6
14	2.05	7.5 (4.88)	6 (3.95)	5.55 (4)	105
21	1.96	8 (5.45)	6 (5.04)	6.75(5.26)	110
28	2.98	8.2 (4.39)	7 (4.02)	6.3 (4.04)	105
28	2.14	9.75(7.01)	7 (4.86)	6.5 (4.88)	135
56	2.60	4.7 (1.38)	3.5 (0.90)	3.3 (1.33)	22
90	2.24	7 (4.14)	6 (3.76)	5.5 (3.8)	92

* The figures in parenthesis indicate the actual increase in size when the measurements are proportioned to the animal's weight, using as a normal standard a rabbit that weighed 2.5 kg. and whose left kidney was 3.2 cm. long, 2.5 cm. deep and 1.9 cm. wide.

The roentgenogram (Fig. 9) of an arterial barium sulphate injection demonstrates the anterior portion of the arterial tree and the absence of any injection in the sac proper. The remarkable degree of atrophy, considering the short period of obstruction, is illustrated in the photomicrograph (Fig. 10).

The best term to describe the unique condition seen in this specimen is pelvic diverticulum. The anterior portion corresponded to that part of the kidney which is supplied by the anterior division of the renal

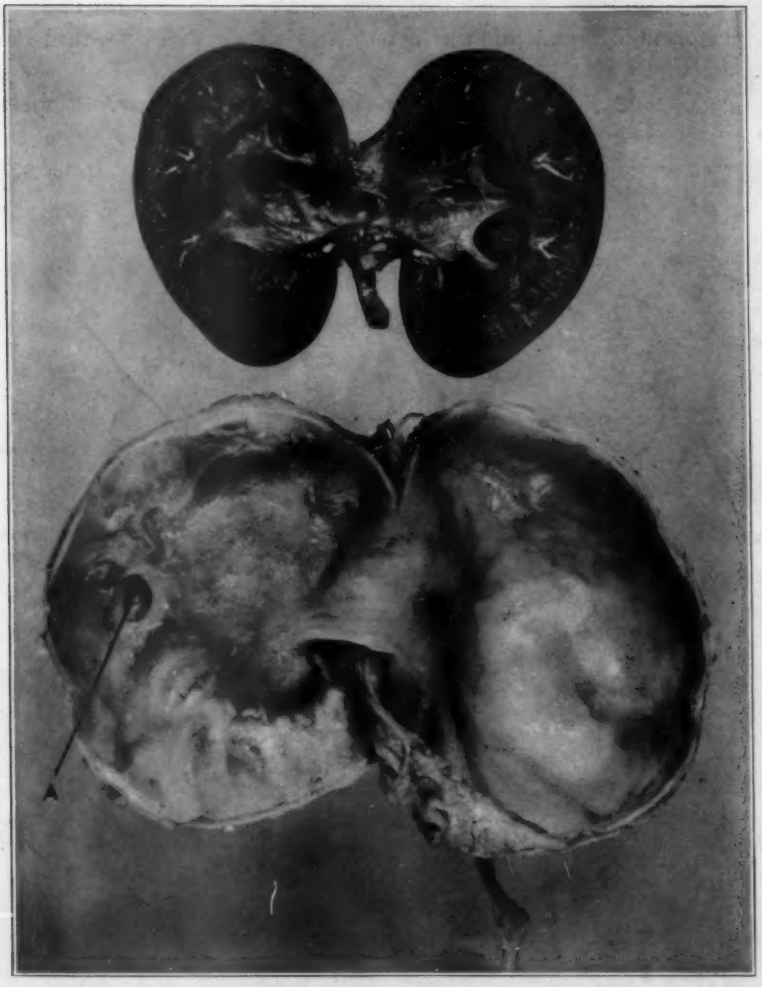

Fig. 12.—Gross specimen to demonstrate the results of arterial ligation in hydronephrosis; upper: sagittal section of twenty-one day hydronephrosis used as a control; lower: twenty-one day hydronephrosis with ligation of posterior branch of the renal artery; opening, *A*, to the outer side of the left half, communicates with the dilated pelvis of the anterior one third of the kidney.

artery. Its blood supply was undisturbed, and, after ligation of the ureter, a hydronephrosis developed therein to the degree usually seen for this period of obstruction. Its dilated pelvis, however, communicated by an opening, 1 cm. in diameter, with an enormous sac that corresponded to that part of the kidney that was infarcted by the ligation of the posterior division of the artery. This portion constituted the diverticulum.

Exactly the same conditions were found in the twenty-one and twenty-eight day specimens (Figs. 12, 13, 14 and 15). The upper kidney in these illustrations represents the hydronephrotic control, and offers a marked contrast to the large sacs seen in the lower one.

Fig. 13.—Twenty-one day hydronephrosis with ligation of posterior branch of renal artery (anterior view); remaining parenchyma in anterior one third of sac has been cut sagitally; the sac or diverticulum, which has been sectioned and laid back, is behind.

The gross, microscopic and roentgenographic studies of this group (seven of twelve rabbits) demonstrate clearly the mechanism by which these unusual conditions are produced. When the posterior branch of the artery is ligated, one third to one half of the kidney undergoes rapid degeneration from anemic infarction. When, in addition, the ureter is ligated, intrapelvic pressure exerted equally in all directions meets less resistance from the degenerated parenchyma of the infarcted area. That the location of these diverticula is dependent on the area of infarction is beautifully illustrated in the specimen shown in Figure 19. In this instance, instead of the entire posterior division of the artery being occluded, only the small branch to the lower pole was sectioned,

and, after twenty-eight days of ureteral obstruction, the intrapelvic pressure, besides producing a hydronephrosis in the normal vascularized portion of the kidney to the degree usually seen after twenty-eight days, caused an enormous diverticulum localized exactly to the area which was deprived of its blood supply.

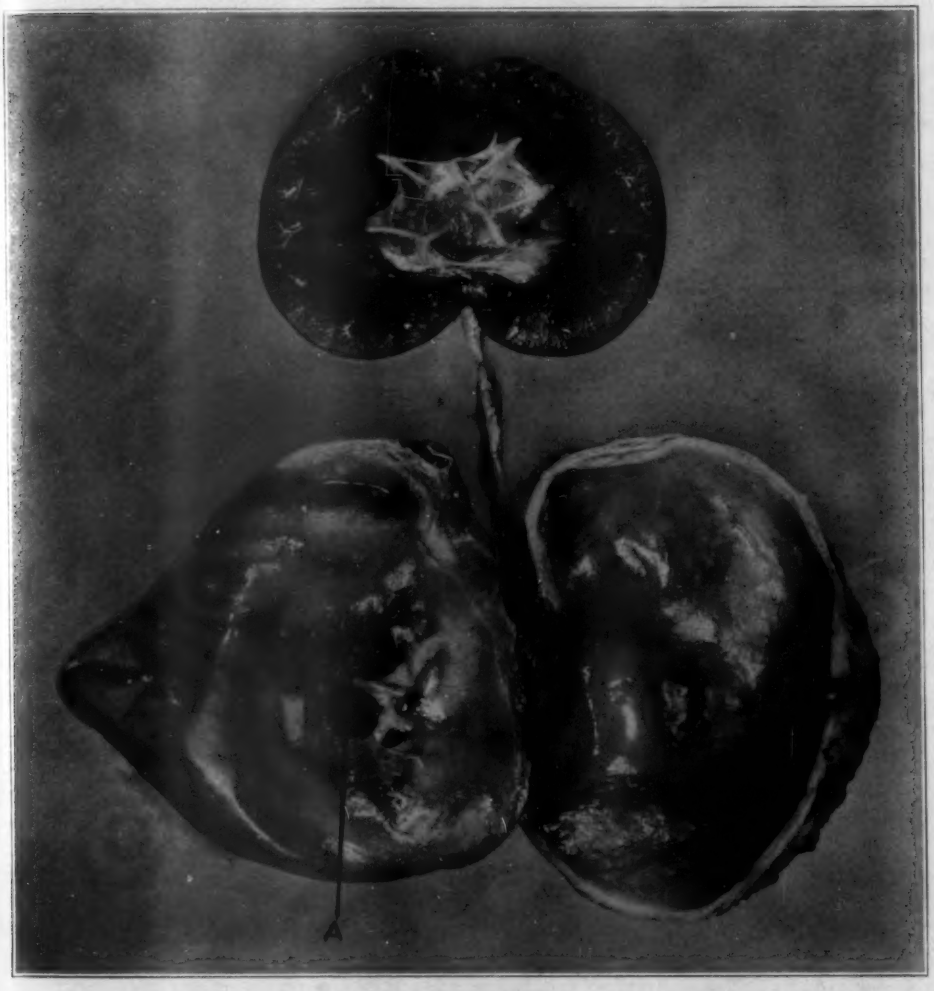

Fig. 14.—Lower: twenty-eight day hydronephrosis with ligation of the posterior branch of the renal artery; fenestrated opening, *A*, in middle of left half communicates with dilated pelvis of anterior portion seen in Figure 13; upper: twenty-eight day simple hydronephrosis used for comparison.

2. The infarcted area undergoes degeneration but dilates equally with the rest of the kidney and forms an integral part of the hydronephrotic sac (two rabbits).

In the fifty-six day specimens of this series, although the infarcted area became a fibrous sac, it did not dilate to the degree seen in the other specimens but remained an integral part of the hydronephrotic pelvis (Fig. 16), which dilated to the degree usually seen after fifty-six days of ureteral obstruction.

The same condition occurred in a rabbit which was discarded from the series to permit the repetition of the experiment with section of the artery instead of ligation (as described under Technic). The hydrone-

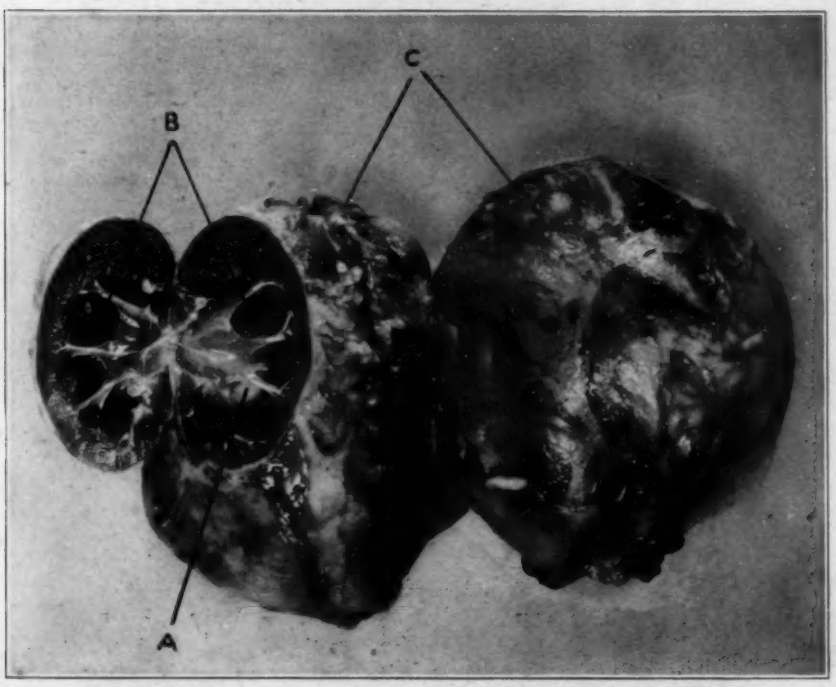

Fig. 15.—Twenty-eight day hydronephrosis with ligation of posterior branch of renal artery (anterior view); parenchyma of anterior one third of sac and sac itself have been cut sagittally; *A*, communication between the dilated pelvis, *B*, and the diverticulum, *C*.

phrotic kidney showed no diverticulum, but, after twenty-one days of obstruction, a degree of dilatation much greater than is usually seen, and the infarcted area, although converted into a fibrous sac, remained an integral part of the dilated pelvis (Fig. 17).

3. Hydronephrosis in the anterior portion of the kidney and, as a result of intrapelvic pressure, perforation of infarcted area (one rabbit). This curious result is illustrated in Figure 18. A perforation of the infarcted area has occurred, and the opening communicates with the hydronephrotic pelvis in the anterior portion of the kidney.

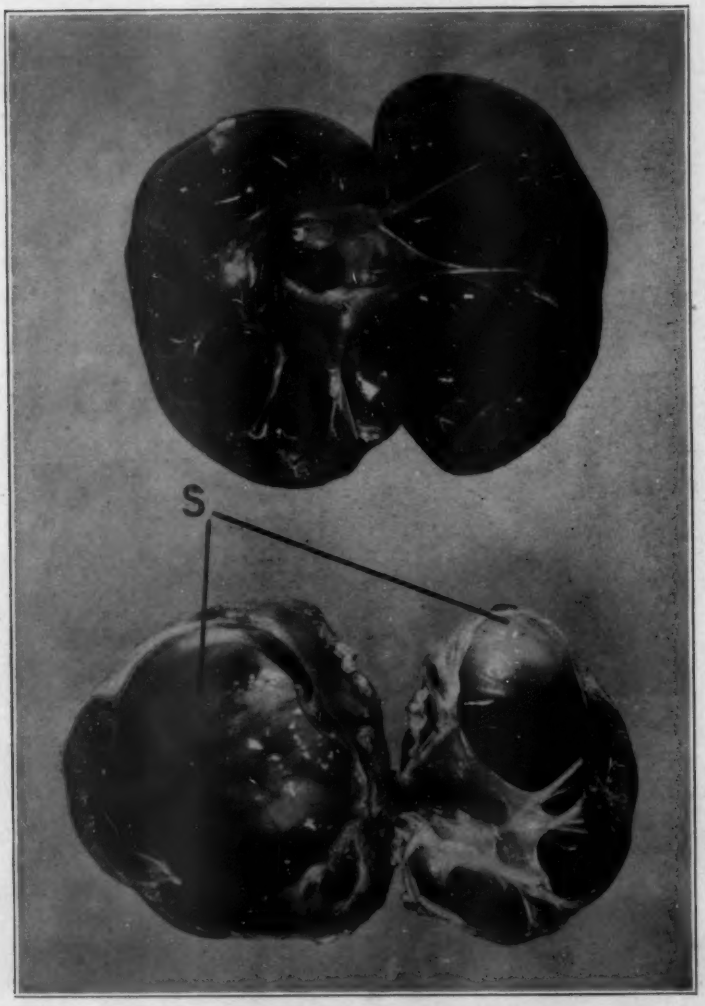

Fig. 16.—Lower: fifty-six day hydronephrosis with ligation of the posterior branch of the renal artery; although the infarcted area becomes a fibrous sac, it does not dilate to the degree seen in the other specimens but remains an integral part of the hydronephrotic pelvis; upper: hydronephrotic control for the same period.

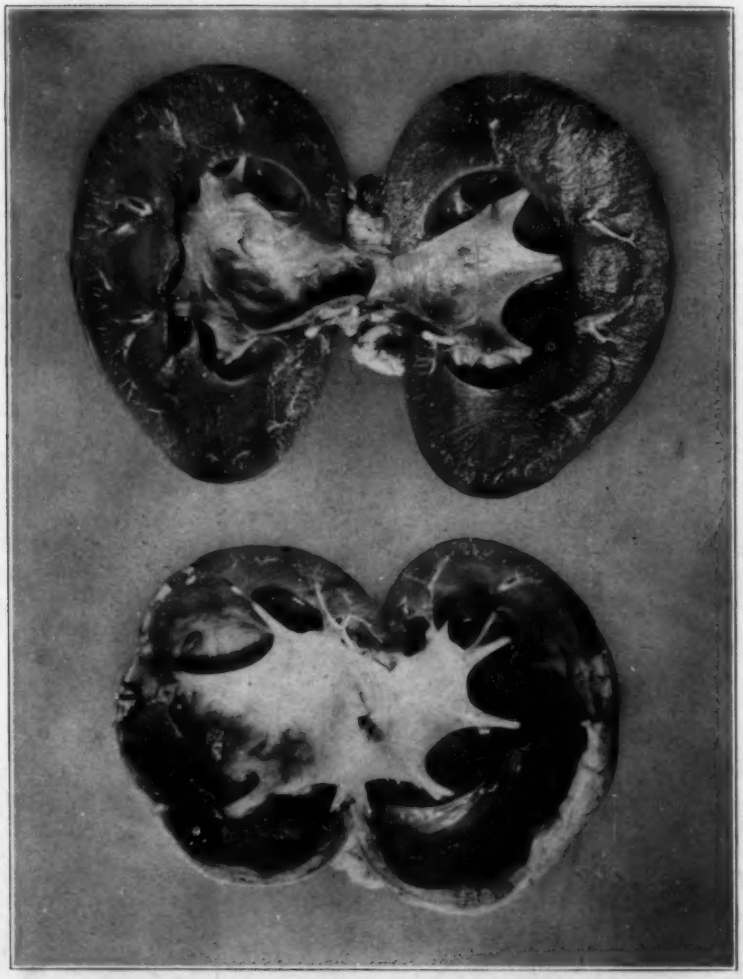

Fig. 17.—Lower: twenty-one day hydronephrosis with ligation of posterior branch of renal artery; upper: simple hydronephrosis for the same period; the hydronephrotic atrophy has been greatly accelerated. This specimen, together with the fifty-six day specimen, shows a marked fibrosis of the infarcted area without diverticulum formation.

4. In two rabbits, there was marked infection of the kidney and hydronephrosis failed to develop. These and one other are the only instances in a large series of animals (dog, rabbit and rat) in which we have completely obstructed the ureter when we have found a primary atrophy. In each case, infection was marked.

The two specimens of the series, after fourteen days of ureteral obstruction, showed no hydronephrosis but a marked focal suppurative nephritis, the parenchyma being studded with small abscesses (Fig. 20).

The other instance occurred in a rabbit after fifty-six days of ureteral obstruction and ligation of the venous collaterals.[7] The kidney,

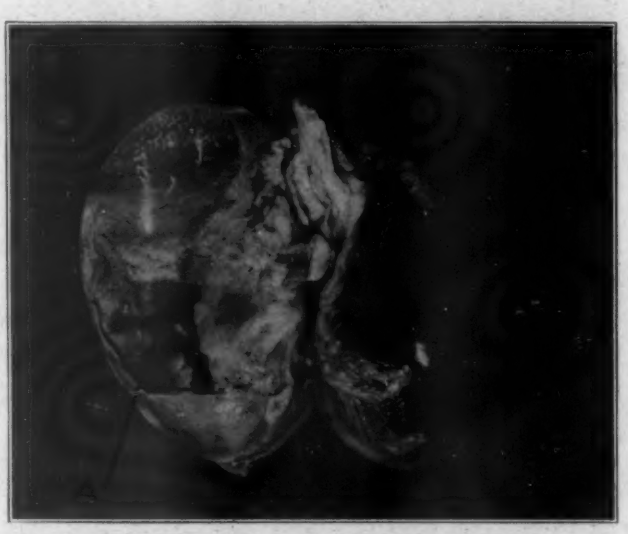

Fig. 18.—Gross specimen of fourteen day hydronephrosis with ligature of posterior branch of renal artery of rabbit; light portion indicates the infarcted area, in the center of which is a perforation with a lumen about 1 cm. in diameter, *A*; specimen demonstrates an unusual effect of the increasing pelvic pressure on the infarcted area as compared to other specimens of this group.

which was about one-half the normal size and in which hydronephrosis had not developed, showed a large abscess of the pyramid. Microscopically, there was an absence of normal renal tissue with complete connective tissue substitution, fibrosis, round cell infiltration and deposit of calcium salts (Fig. 21). The specimen represented a true primary atrophy.

In this connection, it may be said that the opinion that complete ureteral block results in primary atrophy of the kidney has no foundation

7. Hinman, Frank; and Hepler, A. B.: The Effect of Changes in Blood Pressure and Blood Flow on the Rate of Development of Hydronephrosis, II, Partial Compression of the Renal Vein, Arch. Surg., to be published.

Fig. 19.—Twenty-eight day hydronephrosis with ligation of arterial branch of lower pole; effect of the increasing pelvic pressure on the infarcted area, in this case limited to the lower one third of posterior one half of kidney. *A*, communication between dilated pelvis and diverticulum, *B*.

Fig. 20.—Upper: absence of hydronephrosis after fourteen days of complete ureteral obstruction; kidney shows a focal suppurative nephritis; minute abscesses throughout parenchyma; lower: normal right kidney.

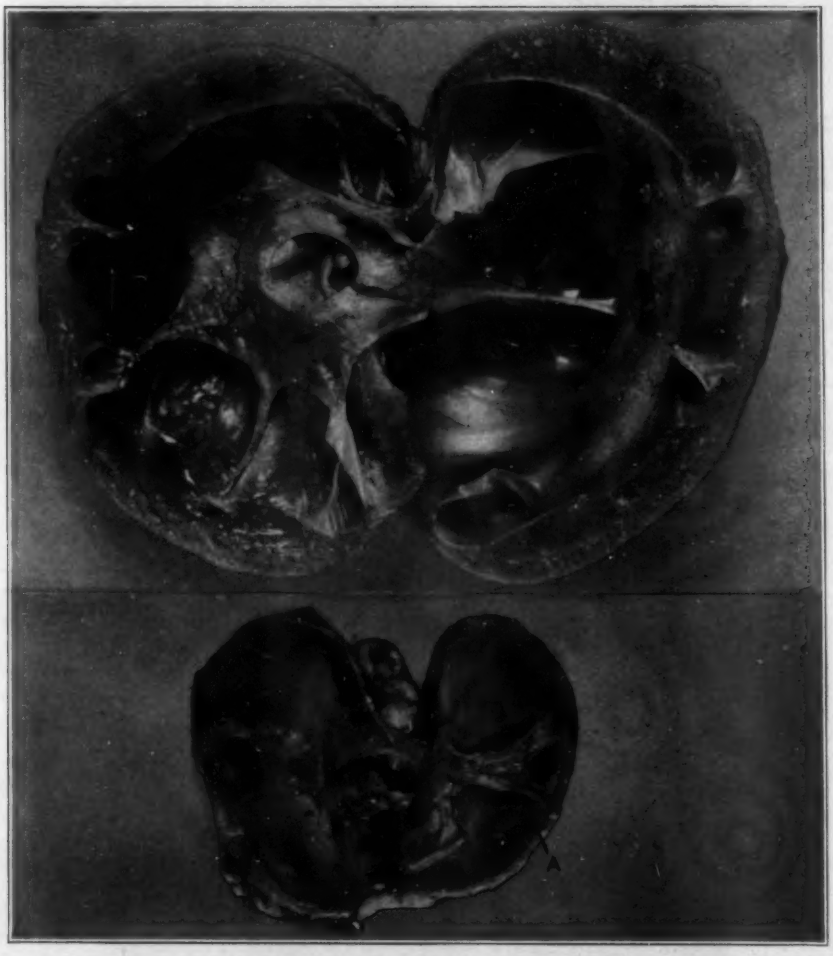

Fig. 21.—Effect of infection on development of hydronephrosis; upper: fifty-six day simple hydronephrosis used for a control; lower: primary atrophy due to infection following ligation of the ureter and destruction of the collateral venous circulation; *A*, abscess (photographs taken on same scale).

in fact. Nevertheless, a primary atrophy occasionally occurs, and our observations indicate that early infection with its resulting anuria is the most important factor in its production.

CONCLUSIONS

1. Due to the almost complete absence of arterial anastomosis, either intrarenal or extrarenal, ligation of the posterior branch of the renal artery causes infarction and throws out of function from one third to one half of the kidney.

2. When this procedure is combined with total ureteral obstruction on the same side, there is produced in a remarkably short time enormous sacculations or diverticula of the infarcted area.

3. This effect is due to the lessened resistance of the degenerated parenchyma to urinary back pressure, and emphasizes, in an exaggerated manner, the significance of blood supply to hydronephrotic dilatation.

4. The absence of hydronephrosis in two specimens of this series, both of which showed a focal suppurative nephritis, confirms our belief in the importance of early infection with its resulting anuria in the production of primary atrophy when the ureter is completely obstructed.

ANGIO-ENDOTHELIOMA OF BONE*

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The question of the recognition of endothelioma as a pathologic entity has always been disputable. The lax requirements for diagnosing endothelioma laid down by Golgi [1] in 1869 and by Kolaczek [2] in 1895 led to widely spread and frequent diagnoses of endothelioma in cases in which no such condition was present. It was Volkmann [3] who protested against these en masse diagnoses of endothelioma. Volkmann pointed out the importance for diagnosis of studying the origin and the development of the tumor rather than the cytology present. The influence of Kolaczek's paper, however, was not offset by Volkmann's arguments. The psychologic factors are evident. Kolaczek's requirement for a diagnosis of endothelioma—the presence of blood between the acinous groups of tumor cells—made this diagnosis popular in complex or uncommon tumors. This diagnostic tendency was applied also to uncommon bone tumors. Howard and Crile's article [4] of twenty years ago is an illustration of it. The details of the morphologic diagnosis of bone tumors of twenty years ago amaze one when we consider our meager knowledge today. Howard distinguishes perithelioma and endothelioma of bone. The endothelioma he further divides into those "derived from the endothelium of the blood vessels and perivascular lymph spaces" and those springing "from ordinary lymph vessels not immediately connected with blood vessels." Such detail is even more surprising when one recalls that until 1924 all anatomists were unanimous that bone and bone marrow are lacking in independent nonperivascular lymph vessels, and only in 1924 Kolodny [5] brought experimental proof that such an assertion is wrong.

Soon a reaction followed among the leading pathologists the world over and, as it happens frequently, the swing went too far. With the exception of a few the most prominent pathologists hesitate to admit that angio-endothelioma of bone is an actual pathologic entity. The

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* From the department of surgery, State University of Iowa College of Medicine.

1. Golgi, Camillo: Sulla struttura e sullo svilappo degli Psammomi, Pavia, 1869.

2. Kolaczek, J.: Ueber das Angio-Sarkom, Ztschr. f. Chir. **9**:2, 1878.

3. Volkmann, Rudolph: Ueber endotheliale Geschwuelste, zugleich ein Beitrag zu den Spiecheldruesen- und Gaumentumoren, Ztschr. f. Chir. **41**:1, 1895.

4. Howard, W. T., and Crile, G. W.: A Contribution to the Knowledge of Endothelioma and Perithelioma of Bone, Ann. Surg. **42**:358, 1905.

5. Kolodny, Anatole: The Relation of the Lymphatic System to the Bone Marrow, Anat. Record **27**:184, 1924.

most outspoken among the latter group, Ribbert,[6] says: "In no instance has it been proven that a so-called endothelioma originated from endothelium." The questions that suggest themselves to an unbiased investigator are the following: "Is angio-endothelioma of bone a true pathologic entity? If so, what is the clinical incidence of this tumor?"

In 1924 I reported[7] a case of multiple angio-endothelioma of the skeleton. The case was entered in the Registry of Bone Sarcoma under No. 291. As the Registry records show, there was considerable opposition to and criticism of the diagnosis by some of the leading consulting pathologists of the Registry, who either spoke of a possible metastatic carcinoma or said that it was impossible to classify the tumor. A similar evasiveness and reluctancy on the part of the pathologists to admit an angio-endothelioma was also observed in the Registry No. 154, which appears to me in every way a typical angio-endothelioma. It is my intention to analyze these two cases with reference to an answer to both questions formulated above.

REPORT OF CASES

Case 1 (Registry No. 154).—E. R., a girl, aged 10 years, suffered a trauma to the right leg below the knee in February, 1921. Two months later pain appeared on walking. Three months after the trauma a physician incised the leg with the diagnosis of an abscess. Nothing pathologic was found and the wound healed readily. The pain persisted. The urine was constantly negative. In May, 1921, a swelling appeared with redness, tenderness and pulsation. After roentgenograms were taken, amputation was advised and refused. In August, 1921, the tumor was curetted twice elsewhere. The wound never healed; the tumor rapidly enlarged, and in March, 1922, an amputation through the middle of the thigh was done. An uneventful recovery followed, and the patient used an artificial limb. In June, 1925, the patient began complaining of extreme headaches and vomiting. The whole train of symptoms of metastases in the brain was encountered. The patient died in July, 1925; no necropsy was permitted but the roentgenograms showed unmistakable lung metastases.

On microscopic examination, at a first glance the tumor cells were seen to be arranged in alveoli and tubules, greatly resembling an adenomatous growth. The thin interalveolar septums formed the base on which the tumor cells were lined. The tumor cells seemed to vary with the maturity of the tumor tissue. In the young areas the alveoli were small and completely filled with tumor cells; no lumina could be made out there. The tumor cells were large, polyhedral, frequently cylindrical, with a well defined cell membrane and with pale vesicular nuclei and minute nucleoli. At a later stage the alveoli showed lumina, frequently filled with intact blood. Multinuclear tumor cells could easily be found. At a still later stage the tumor cells were undergoing degenerative changes. Vacuolization and hydropic changes were seen, but the clear cytoplasm still retained the affinity toward basic and acid stains. The most interesting areas were those where alveoli filled with intact blood were lined by

6. Ribbert, Hugo: Geschwulstlehre, Ed. 2, Bonn, 1914, p. 245.

7. Kolodny, Anatole: A Case of Primary Multiple Endothelioma of Bone, Arch. Surg. 9:636 (Nov.) 1924.

a single row of tumor cells exceedingly well simulating blood vessel endothelium. Not infrequently fields were found where the origin of the tumor cells could be traced to normal appearing endothelium of blood vessels. Blood spaces were seen showing on one side of their wall normal endothelium while on the other side the endothelium had begun to proliferate and to pile up toward the lumen. Sections taken through the edge of the tumor bordering on the grossly intact bone showed that the tumor did not extend into the adjacent

Fig. 1 (Registry No. 154).—Osteolytic tumor of tibia; the involvement does not extend beyond the epiphyseal line.

bone so that the shadow of the bone destruction seen in the roentgenogram corresponded with the actual histologic extent of the tumor. No bone production could be noticed in sections through the tumor mass.

CASE 2 (Registry No. 291).—This case was reported by me in 1924. The salient features of the clinical history and the histology of the tumor were as

follows: A woman, aged 48, in February, 1923, began having a dull ache in the left hip, in the right leg and in the back between the shoulders. Roentgen-ray examinaion showed osteoblastic tumors on the right fibula, on the left tuber ischii and on both scapulae. After an exploratory operation in March, 1923, the patient was put on radiation therapy, without any noticeable result. The patient died in November, 1923, and the necropsy revealed tumors throughout most of the bones, with metastases to the lungs and to the mediastinal lymph nodes. The characteristic features of the microscopic examination were the same as in Case 1, with the main exception that here the tumor spread through

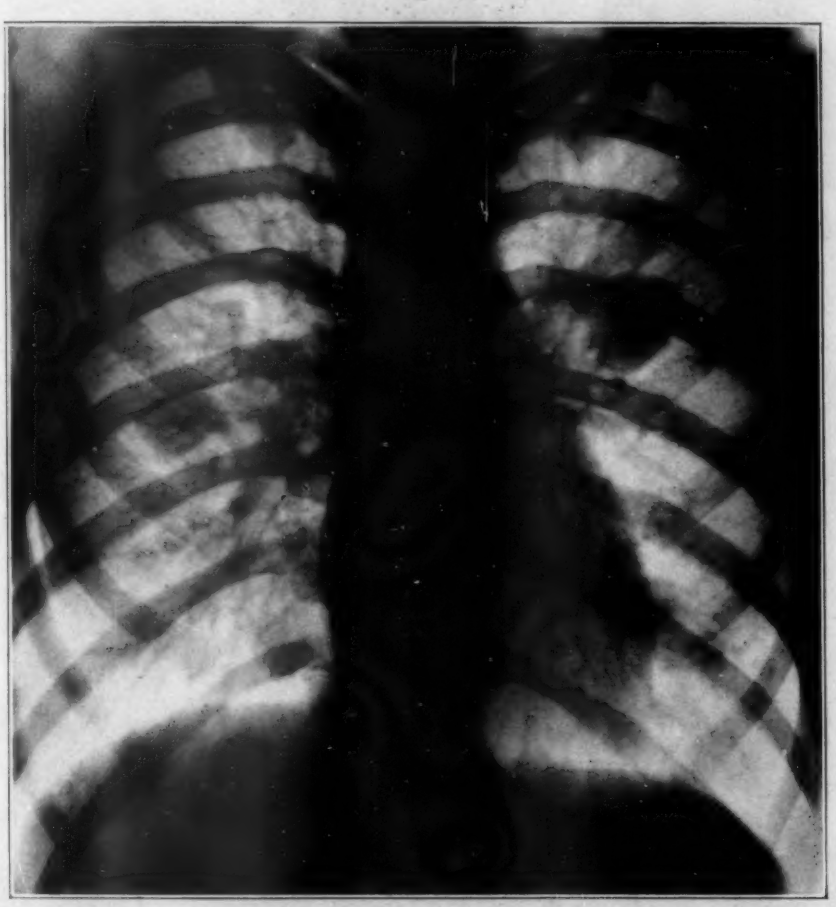

Fig. 2 (Registry No. 154).—Pulmonary metastases, in June, 1925.

seemingly normal bone. Well differentiated and low grade new formed bone could be seen here in abundancy. A feature common to both cases was that the strands of tumor were intimately connected with the supporting stroma and the surrounding tissue and not separated from it by means of endothelial cells lining the connective tissue spaces as it is always seen in carcinomatous metastases. The blood supply in both tumors alike consisted of arterioles and capillaries embedded in the connective tissue framework bounding more or less large areas of tumor alveoli. These vessels were normal in every respect.

COMMENT

The fact that the tumor cells could be traced to the endothelium of the blood vessels, the morphologic features of the tumor cells, the intimate attachment of the groups of tumor cells to the surrounding tissue and the frequent occurrence of intact blood in the alveolar lumina, all these features taken together speak for angio-endothelioma.

Fig. 3 (Registry No. 291).—Fibular tumor, distinctly osteoblastic.

The proliferation of the endothelium by itself is in no way characteristic of endothelioma. It is frequently encountered in carcinoma in which tumor cells fill the lymphatics and blood channels. It is then a normal reaction to the presence of foreign tissue. But in carcinoma the difference between the proliferating endothelium and the cancer cells is so striking that it cannot be overlooked.

The morphologic features of the tumor cells in both cases are characteristic of endothelial cells. The clear cytoplasm with the well defined cell borders and distinct cell membrane, the small pale vesicular nucleus and the multiple minute nucleoli are different from epithelial cells, which usually show granular opaque cytoplasm and bulky acidophil nucleoli. It is realized that the tendency prevailing among some pathologists to base a diagnosis of a pathologic tissue on the morphologic features of a few cells is, to say the least, hazardous. However, the morphologic features of the tumor cells when taken together with the other data are of a greater value in diagnosis.

Fig. 4 (Registry No. 291).—Osteoblastic tumor on left tuber ischii.

The intimate attachment of rows of tumor cells to the surrounding stroma speaks against carcinoma. In the latter, the groups of tumor cells are separated from the surrounding stroma by means of endothelial cells lining the invaded connective tissue spaces. The most ardent opponent of the recognition of endothelioma as a separate entity, Ribbert, insists that "das Festhalten an der bindegewebigen Unterlage" is not a characteristic feature of endothelial cells, because there are instances, when endothelial cells readily loosen from the underlying stroma in the walls of the lymphatics and the lymph sinuses of the lymph nodes.[8] It is obvious, however, that similar exceptional cases do not

8. Ribbert, Hugo: Geschwulstlehre, Ed. 2, Bonn, 1914, p. 238.

negate the fact that while in carcinoma the groups of tumor cells can be readily brushed out from their supporting stroma, in tumors called endothelioma there is an intimate organic connection between the tumor cells and the surrounding stroma.

The presence of blood in the lumina of the alveoli is the most deceptive sign in diagnosing endothelioma. This feature has been the

Fig. 5 (Registry No. 291).—Osteoblastic tumor on left scapula, showing sharp contours of tumor.

stumbling block of those who are inclined to classify uncommon vascular tumors as endothelioma; it has been looked on as the best evidence that the tumor has originated from the endothelium. Volkmann was the first to emphasize that the presence of blood in the centers of acinous

groups of tumor cells is in no way evidence that the tumor cells originated from the endothelial lining of blood capillaries. It is a matter of fact that a hemorrhage into the tumor from traumatized thin walled capillaries may lead to forcing of blood between alveolar like groups of tumor cells. Such blood may simulate on section blood spaces. However, the walling of circulatory spaces by tumor cells, taken together with other criteria, strongly supports the diagnosis of angio-endothelioma.

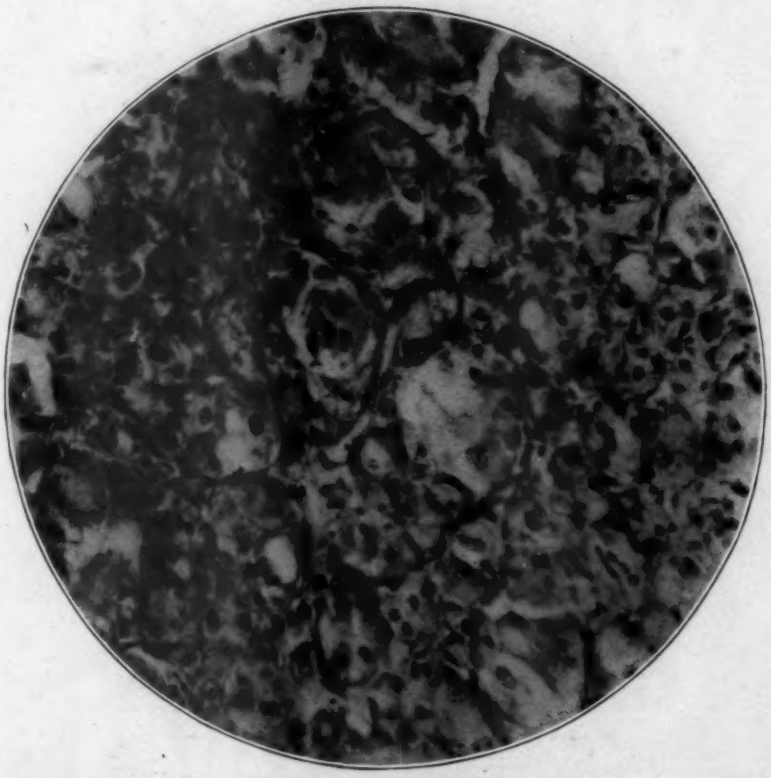

Fig. 6 (Registry No. 154).—Alveolar arrangement of tumor cells; some of the alveoli have lumina filled with intact blood.

The described points of the microscopic findings lead to the belief that the diagnosis of angio-endothelioma in these two cases is well founded. Of course a rigid criticism of the evidence discussed above might lead one to think that each of the features enumerated is by no means an infallible criterion of endothelioma; but on the whole all these features evaluated together speak clearly for this diagnosis. Hence, these two cases clearly answer in the affirmative the question, Is angio-endothelioma of bone a true pathologic entity?

These two cases found in the material of the Registry—a series of tumors well above 650 cases—furnish some evidence as to the question of the frequency and clinical incidence of angio-endothelioma of bone. Such a rarity of this type of tumor strongly contradicts the reports found in the literature. In the frequently quoted paper of Howard and Crile [4] are reported twenty-three cases of endothelioma of bone, mostly of the angio-endothelioma type. Critical research seems to justify my skepticism regarding the true nature of most of the cases

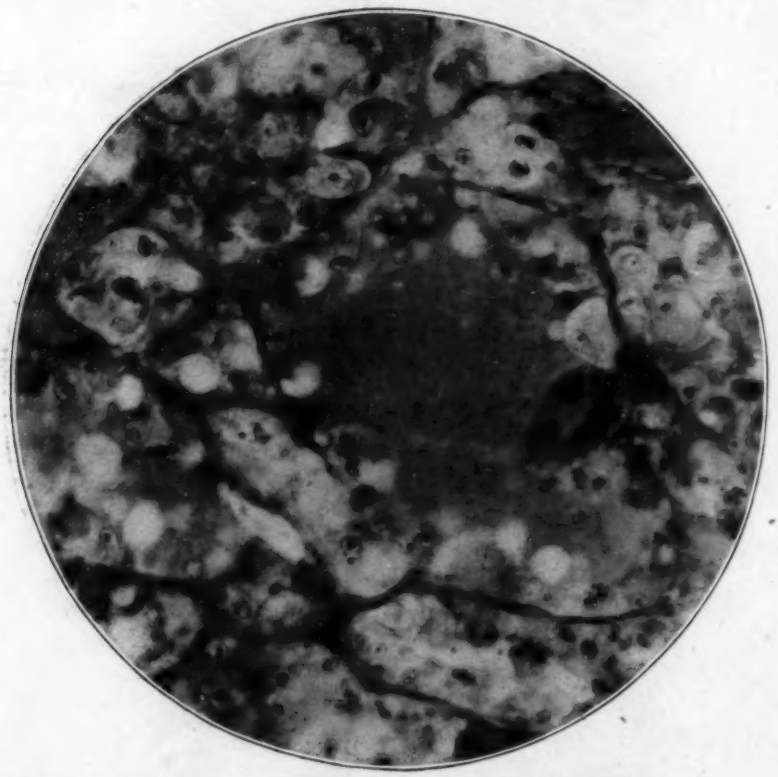

Fig. 7 (Registry No. 154).—Blood channels lined by tumor cells.

reported. The multiplicity of the tumors in the majority of the cases reported, the spreading of the growth along the marrow cavity in most cases, the localization of the tumors, the carcinoma age of the patients, all suggest the possibility of carcinomatous metastases in some of the cases. That multiple endotheliomas of bone do occur is fully attested, but the multiplicity of the tumors in the majority of the cases reported by Howard and Crile strongly raises the suspicion of metastatic carcinoma. The same doubt in the diagnosis of endothelioma is supported by the fact that the growths spread along the marrow cavity in most

cases. This feature is typical of skeletal carcinoma. It is known that the bones under constant physiologic stress, the axial skeleton, usually become involved first in metastatic carcinoma. In Howard and Crile's cases the axial skeleton was involved in one third of all cases. As to the age, one can frequently read in the literature that bone endothelioma is at variance with bone sarcoma and in accordance with carcinoma. This statement has been based on doubtful endotheliomas of bone. As a matter of fact angio-endothelioma of bone is an exceedingly rare tumor

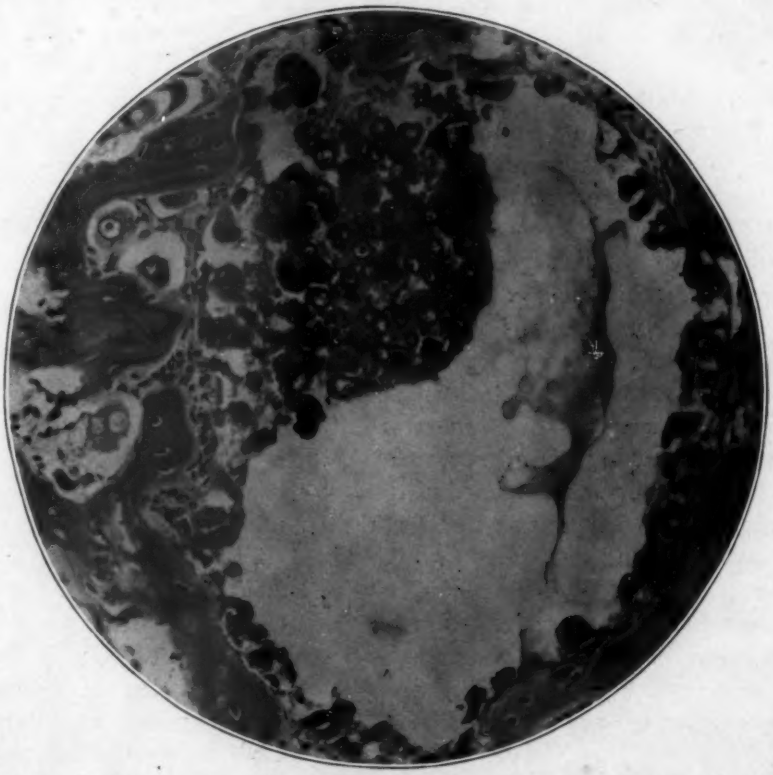

Fig. 8 (Registry No. 291).—Proliferation and piling up of blood channel endothelium.

so that no rules as to the age can be made. On the other hand in Howard and Crile's series, if one excludes the three patients less than 20, who probably had Ewing's tumors, the average age will be 60 years for men and 54 for women. This age is well in accord with the carcinoma age for men and women. If one adds to all these considerations the fact that a necropsy was performed in only six cases out of the twenty-three reported and that the cases belong to a period when modern diagnostic roentgenology was unknown, one is impressed with the fact that it is not safe to draw conclusions about the natural history

of endothelioma of bone from the cases reported in the paper of Howard and Crile.

Ewing, who has probably constributed more to the knowledge of malignant bone tumors than any other living pathologist, describes three varieties of endothelioma of bone: (1) multiple endothelioma, (2) solitary angio-endothelioma and (3) diffuse endothelioma, known as Ewing's tumor.[9] It is felt that the inclusion of these three groups under a common term "endothelioma" is ill founded. An analysis of these tumors makes one wonder whether the name "endothelioma" is not the only feature that these groups of tumors have in common. The course, the clinical incidence, the prognosis and the morphology are entirely different in Ewing's tumor from what they are in those grouped by Ewing under the first two headings. So, while there are about fifty cases of Ewing's tumor in the Registry material, only two cases and certainly not more than three are found of the first two groups. Further, while Ewing's tumors are known to be susceptible to radiation therapy, whether roentgen ray or radium, the tumors of the first two groups are not influenced by radiation. And, finally, the morphology of these tumors is different. There is no sufficient proof on hand to support the contention of Ewing, that "diffuse endothelioma" (Ewing's tumor) is really an endothelioma. The name "diffuse endothelioma" offered by Ewing for these tumors is just a working hypothesis on which the natural history of these tumors is to be built. Meanwhile, because of Ewing's immense influence in this country the name "diffuse endothelioma" has led among the average pathologists to a still greater confusion in the dark and unexplored territory of endothelioma of bone. The term "Ewing's tumor," or "endothelial myeloma," is for the present to be preferred to "diffuse endothelioma." In explanation of the failure of radiation therapy in angio-endothelioma of bone in comparison with the remarkable susceptibility to radiation of Ewing's tumors, Ewing says "endothelioma yields different results at different periods of life."[10] Not the age of the patient but the type of the tumor is decisive as far as the influence of radiation in malignant bone tumors is concerned. Patient 1 (Registry No. 154), a girl aged 10 years, with an angio-endothelioma of bone, failed to respond to radiation in the same way as Patient 2 (Registry No. 291), a woman, aged 48, with an angio-endothelioma of bone; no case of Ewing's tumor whatever the age remains indifferent to radiation.

There is another feature which in the opinion of Ewing is common to all varieties of endothelioma of bone. This feature is the influence

9. Ewing, James: A Review and Classification of Bone Sarcoma, Arch. Surg. **4**:487 (May) 1922.

10. Ewing, James: A Review and Classification of Bone Sarcoma, Arch. Surg. **4**:493 (May) 1922.

of the tumor on the affected bone. Ewing emphasizes that bone absorption and bone destruction are typical of endothelioma of bone. Since the present paper is dealing solely with angio-endothelioma it is too far afield to discuss this statement of Ewing in relation to Ewing's tumor. With reference to angio-endothelioma this observation of Ewing does not hold true. Not only was bone production present in Case 2, as is seen from the roentgenograms, but also in the frequently quoted case of multiple endothelioma of Marckwald [11] there was distinct new bone formation on the scapula and os ileum and a prominent sclerosis of the involved long pipe bones. It is believed that attempts to classify tumors of bone according to bone production or destruction are ill founded. As a matter of fact one rarely can find a malignant bone tumor in which both bone production and destruction are not present to a greater or lesser degree. One of the important accomplishments of the Registry of Bone Sarcoma is clarifying the fact that in classifying bone sarcoma no attention should be paid to the osteoblastic or osteolytic character of the tumor. There is a pressing need of revising the present day views of pathologists on the influence of a malignant bone tumor on the affected bone. The more one studies the unsurpassed material of the Registry the stronger one feels that differentiation between osteoblastic and osteolytic tumors and between reactive new bone production and tumor bone formation lacks a scientific basis. If such a difference between reactive new bone and tumor bone does exist the present day methods of studying bone are entirely inadequate to bring it out. As a matter of fact it is impossible for anybody to tell reactive new bone from tumor bone with certainty. In callus after fracture one frequently encounters low grade new bone while, on the other hand, tumor bone may be found in pulmonary sarcomatous metastases that can serve as illustration of normal histology of bone.

CONCLUSION

The two cases analyzed show that angio-endothelioma of bone is a true pathologic entity, which is exceedingly rare. It should be recognized that unless the diagnosis of endothelioma of bone is arrived at only after all the evidence is clear and conclusive, endothelioma will persist to be the graveyard of those uncommon complex tumors of which the present day knowledge is extremely meager. Not by dodging and sidestepping the question of recognition of angio-endothelioma of bone as an existing disease but by careful and intensive study of similar tumors and by elimination of all those which are of questionable origin will this be accomplished.

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11. Marckwald: Ein Fall von multiplem, intravasculaerem Endotheliom in den gesammten Knochen des Skelets, Virchows Arch. f. path. Anat. **141**:128, 1895.

SUBSEQUENT NOTE

After the proof of this article was returned by me, I noticed in the proof of Charles L. Connor's article "Endothelial Myeloma, Ewing" (in this issue of the ARCHIVES OF SURGERY) the following footnote: "It must be mentioned that the paper by Kolodny (A Case of Primary Multiple Endothelioma of Bone, Arch. Surg. **9**:636 [Nov.] 1924) is entirely misleading, the peculiar tumor reported by him having *no features in common with endothelial myeloma*" (italics mine). This footnote proves exceedingly well the statement I have made above that the name "endothelioma" used for Ewing's tumor frequently leads to a confusion of Ewing's tumor with angio-endothelioma. In reporting my case I have not contended that it had anything in common with Ewing's tumor (endothelial myeloma). What one concludes from this misunderstanding is that the name "endothelioma" used in cases of Ewing's tumor is misleading and confusing for the clinician and pathologist not expert in bone tumors.

BONE FORMATION IN OSTEOGENIC SARCOMA

TELEOLOGIC CONSIDERATIONS *

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It has been said that the bone cell is the most physically stable and the most biologically labile of all the cells in the animal body. This is substantially true: while the bone cell gives permanent form and rigidity, there is no cell in the body that is more subject to the influences of variations in diet, to the effect of chemicals and to pathologic processes.

A conspicuous concomitant of bone disease is bone production. Bone production may occur simultaneously and alongside of bone, showing recessive changes. Production of new bone is a response to bone invasion from many causes. It is strikingly absent in a large group of diseases of bone, among which should be mentioned the cystic degenerative processes and the so-called deficiency diseases, myeloma, metastatic bone tumor and a large group of primary osteolytic sarcomas.

In those processes in which new bone occurs, the manner and form of this new bone varies with the type of invasion. New bone formation is usually an attendant on reparative processes in bone. The new bone formation of osteogenic sarcoma is dissimilar to that produced by other causes.

In a previous article [1] the statement was made: "In examining the roentgenogram of bone sarcoma, we must realize that we are not looking at the roentgenogram of the tumor, but of a bone struggling, in its way, to protect itself from the invasion of disease." This point of view impressed itself on my mind from the study of serial roentgenograms of an osteogenic sarcoma over almost the entire period of its life history.

This conception led to the idea that the malignancy in osteogenic sarcoma resides in the soft tissue structure and that the new bone formation is secondary and not necessarily part of the malignancy. More recent studies into the nature of new bone formation in osteogenic sarcoma have tended to corroborate this belief and have led to the further inference that not only is the new bone formation the product of secondary reaction on the bone forming cells, but also that the new-formed bone is Nature's expression of her attempt to limit the neoplastic invasion.

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* From the Hospital for Joint Diseases.

1. Eising, E. H.: Diagnosis of Sarcoma in Bone, J. A. M. A. **80**:1429-1432 (May 19) 1923.

Sarcoma occurring in the soft tissues sometimes presents masses of cartilage or of bone. These masses are usually small and rarely go on to complete development. Areas of bone occur in many tumors of metaplastic origin, especially those of the parotid, testis and ovary. Bone also occurs as a terminal stage of calcification in the walls of arteries. This type of bone production is considered a metaplasia of connective tissue and is a very different formation from the bony structure of osteogenic sarcoma.

Nowhere have I been able to find evidence that bone is a direct product of the transformation of sarcoma cells. Bone production seems not to be inherent in sarcoma cells themselves but appears to be an incident contingent on the point of origin of the tumor growth.

In one large group of bone sarcomas, there is not only no bone formation but what seems to me of far greater interest a definite osteolytic or bone absorptive activity that destroys previously existing bone.

In the embryo, bone development is an orderly process starting in a matrix of embryonal connective tissue. Minute vessels begin to appear, arranged in a direction mainly parallel with the axis of the structure destined to become bone. In each case a layer of bone cells is laid about a vessel and completely surrounds it. Another layer of bone cells is then laid from within, until six or eight such layers have been formed about each vessel. These structures are called "osteons" and are destined eventually to become haversian systems, the original vessel remaining patent and representing the haversian canal. Innumerable such systems lying in close contact comprise the substance of compact bone.

These minute budding vessels therefore represent the first and the most active osteogenic agent in the embryo. This function is not lost in adult life.

The periosteum, developing simultaneously, is formed from a different structure and appears not to exert any direct osteogenic function in the formation of embryonal bone.

The roentgen ray is our chief means of studying the growth of bone tumor in vivo. This method is beset by difficulties of interpretation which readily lead to error, even in the hands of the most experienced. In numerous instances, however, it yields us more knowledge as to the nature of a given tumor than does the histologic examination of a casual specimen.

Ewing[2] has recently stated,

> There are comparatively few bone tumors that cannot be somewhat accurately classed by means of roentgenograms and clinical signs, and I have often found that the conclusions drawn from the roentgenograms lead to rather more serviceable results than the study of fragments of tumor tissue taken under difficulties.

2. Ewing, J.: Diagnosis of Cancer, J. A. M. A. **84**:1-4 (Jan. 3) 1925.

Speaking of biopsies in bone tumor, he states,

> The portion of tissue removed fails to yield a satisfactory conclusion or even leads to errors that might be avoided by other methods of study.

In those osteosarcomas in which a morphologic study shows malignancy, the differential features determining malignancy reside in the appearance of the soft tissue elements and not in the new-formed bone.

Bone production, in osteogenic tumor, occurs in a lawless manner of growth and is not subject to the biologic laws of normal bone growth. This tendency to abnormal growth of the new-formed bone is probably due to the fact that it develops in a mass of soft tumor tissue, which itself is lawless in its growth. In any given histologic field of osteogenic sarcoma, it is impossible to conclude from the appearance of the new-formed bone that the section is part of a malignant growth. The diagnosis of malignancy rests solely with the cells of the soft tissue.

In this study it is not essential to discuss the various theories of bone production. There are, however, certain fundamental concepts that apply to normal bone formation which must also apply to bone formation in a malignant environment.

It has been stated by Wells,[3] Freudenberg,[4] Freudenberg and Gyorgy [5] and others [6] that before ossification or calcification can occur, there must first be a hyaline matrix; this is true under any conditions of bone formation.

Another essential is the existence in the blood, and presumably in the tissue fluids, of a solution of calcium ions and biphosphate ions in such a state that their solubility product is just below the precipitation point of tricalcium phosphate, the essential ossification of each cell being purely a biochemical problem and by no means well understood.

From the embryologic and physicochemical standpoints, therefore, the fundamental essentials for the production of bone are: (1) the production of a vascular system of budding vessels having the bone forming potentialities of the cells of the haversian canals, and (2) the elemental constituents of bone in an available form. These elements of bone production appear to be present in the formation of bone in osteogenic sarcoma.

In the nonossifying or better named "osteolytic" types of bone sarcoma, it seems fair to assume that a reverse biochemical process occurs, leading to decalcification.

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3. Wells, H. G.: Harvey Lecture, 1910-1911, in Chemical Pathology, Ed. 4, 1900, Chapter 17.
4. Freudenberg: Monatschr. f. Kinderh. **22**:726, 1921.
5. Freudenberg and Gyorgy: Biochem. Ztschr. **127**:299, 1921.
6. Gyorgy, P.: Monatschr. f. Kinderh. **22**:723, 1921.

The bony structure of osteogenic sarcoma is too varied to allow of detailed description. Anatomically it varies from the compact ivory-like mass of sclerosing osteogenic sarcoma to the softer and sometimes pulsating telangiectatic type with an overgrowth of blood vessels. Between these two are all grades of predominance of fibrocellular tissue, as in the so-called periosteal sarcomas.

In the sclerosing osteogenic sarcoma, the marrow cavity becomes obliterated and the shaft presents a fusiform swelling. The bone cells are of nearly normal structure but are unusually compact and dense, enclosing small areas of sarcoma cells. The growth is slow and metastases occur late. This type of bone sarcoma, I believe, is Nature's supreme attempt by means of excessive and orderly calcification to lock off the malignancy.

It is possible that the chronic nonsuppurative sclerosing condition known as osteomyelitis of Garré may after more careful study, be found to be sclerosing osteogenic sarcoma in which the sarcomatous process has been successfully checked.

In the more cellular types of osteogenic sarcoma maceration leaves bony trabeculae radiating out from the shaft, or globular masses resembling exostoses, or isolated bony areas that are entirely removed from the main structure.

In the osteoid tumors, the cells are reduced in number and are apparently partly or completely inclosed in lamellae of hyaline, partly ossified material. Areas of cartilage are often mingled with the osteoid tissue and many phases of the transformation of cartilage and osteoid tissue into bone appear.

Most tumors fail to carry the development of bone to completion.

The studies of Berg and Thalhimer [7] and Meyer and Wehner [8] and others lay especial stress on bone produced by the osteoblasts lining the haversian canals. The activity of these cells cannot be ignored, especially in the early life history of bone sarcoma.

The osteoblasts in the haversian canals seem to respond early to the chemical irritation of sarcoma growth. In fact, it seems to me quite likely that the origin of the vertical rays seen in the roentgenogram of early sarcoma is from this source.

In a case of osteogenic sarcoma of the humerus seen at a very early period of its growth, the roentgenogram gave the appearance of a medullary growth with numerous fissures and fragmentation of the cortex. These fissures appeared to follow the general grouping of the haversian canals and were probably produced by the formation of new bone in them. The later history of this growth showed it to be def-

7. Berg, A. A., and Thalhimer, W.: Ann. Surg. **67**:331 (March) 1918.
8. Meyer and Wehner: Am. J. Orthop. Surg. **12**:213-244 (Oct.) 1914.

initely of the osteogenic and not of the medullary type of tumor. It cannot be said definitely that the origin of these rays is in the haversian canals, but it seems unlikely that their origin is in the periosteum, whose characteristic function is to lay down new bone parallel to the axis of the shaft and not at right angles to it.

A careful study of the roentgenogram will sometimes show the periosteum lifted for a considerable distance beyond the cortex and the vertical rays reaching outward toward it but not yet meeting it; this suggests a soft tumor growth, which lifts the periosteum from the cortex, which later becomes invaded by spicules of bone emanating from the cortex.

It is quite conceivable that these rays represent ossification about vascular trunks formed in the soft tumor mass, exactly as the osteon is formed in the embryo, following in the wake of the soft tumor mass.

The egg-shell crepitation that many of these tumors present could be satisfactorily accounted for by the crunching under slight pressure of these fine peripheral calcified spicules of bone.

The formation of vertical rays occurs under certain conditions not due to sarcoma. I have seen it in chronic osteomyelitis and also in a chronic fibrous anchylosis of the elbow. In neither case were the rays as well developed as in sarcoma.

The periosteum, doubtless, is a contributor to the newly formed bone, but I believe to a far less extent than has hitherto been presumed.

The gross specimen on section will sometimes show the periosteum lifted from the cortex for a great distance. The intervening space is occupied by tumor tissue, through which run interdigitating spicules of bone between the cortex and the periosteum. The newly formed bone is much more profuse and denser in the region nearer the cortex than in that near the periosteum. Large vascular cavities are seen in the telangiectatic types.

In growths of large size, the periosteal capsule is rarely complete. Some of these tumors grow with an astonishing speed. The roentgenograms taken at intervals of two or three weeks demonstrate a slowly advancing bony structure invading, in a centrifugal direction, the preformed tumor mass.

I question, with Codman,[9] the propriety of the term "periosteal" as applied to osteogenic sarcoma. Two of the cases of osteogenic sarcoma that I observed seemed to have had their origin in the medullary cavity.

The metastases in osteosarcoma consist in the main of a cellular sarcomatous stroma, occasionally containing small areas of cartilage or bone. Bone when present is rarely completely developed and usually

9. Codman, E. A.: Nomenclature Used by the Registry of Bone Sarcoma, Am. J. Roentgenol. **13**:105 (Feb.) 1925.

does not achieve important proportions as in the parent growth. If the osteogenic function resided in the metastasizing sarcoma cells, it would be logical to expect to find an abundance of fairly well developed bone in a large percentage of such metastases. This, however, is not the case.

These masses of bone or cartilage found in metastases unquestionably form after the lodgment of the sarcoma cells in their resting place. They are probably caused by the carrying away with the sarcoma cells of minute masses of osteoblastic material at the moment of the liberation of the sarcoma cells.

On these premises I have assumed the following hypothesis:

1. Sarcoma in bone is a malignancy of the softer structures and connective tissues in bone progressing in the matrix and along the pathway of the haversian canals and blood vessels.

2. The new bone proliferation in osteogenic sarcoma is a secondary process and is the result of an attempt at the establishment of a natural barrier to the intrusion of the neoplastic process.

If this hypothesis is true, it should be possible to demonstrate its truth, in some measure, roentgenographically. This may at first appear simple, but it is beset with the difficulties and pitfalls of interpretation that surround roentgenologic diagnosis.

Fig. 1.—Appearance of comminuted fracture of left femur in woman, aged 46, who fell while walking on the street, Jan. 14, 1919, and was carried to the Harlem Hospital; a cast was applied. A more careful examination of the roentgenogram at this time should have revealed that the bone was cystic and that the fracture was pathologic. The cast was removed after eight weeks and the patient walked with some pain.

Fig. 2.—Appearance of femur shown in Figure 1, June 2, 1921, when patient came to clinic of Hospital for Joint Diseases, complaining of swelling, instability and some pain; a badly united fracture in huge mass of new-formed bone, which seemed cystic. The use of a brace was advised, but the patient disappeared from observation.

Fig. 3.—Appearance of femur shown in Figures 1 and 2 three and one-half years later when patient went to Presbyterian Hospital; huge giant cell tumor involving lower two-thirds of femur; fracture entirely healed, leaving no evidence of its previous existence. The reason for including this case in a series of osteogenic tumors is the peculiar bony structure on upper and inner aspect of tumor. At this point one of the large vacuoles had become fissured. The contents of the vacuole had evidently extruded into soft tissues and new bone had formed about the extruded material, preventing further invasion of tissues. This new bone was apparently not formed by the periosteum. The periosteum was not lifted and the fissure in the cortex was distinctly seen. This case is strongly suggestive of the barrier function of new bone.

Fig. 4.—Fragmentation of cortex and appearance of medullary growth in girl, aged 7 years, two weeks after she was struck on shoulder while playing, when she was brought to clinic of Hospital for Joint Diseases; painful swelling present.

Fig. 5.—Appearance of shoulder shown in Figure 4 with further fragmentation, production of pathologic fracture and lifting of periosteum from cortex.

Fig. 6.—Shoulder shown in Figures 4 and 5 with great proliferation of new bone and consequent healing of fracture.

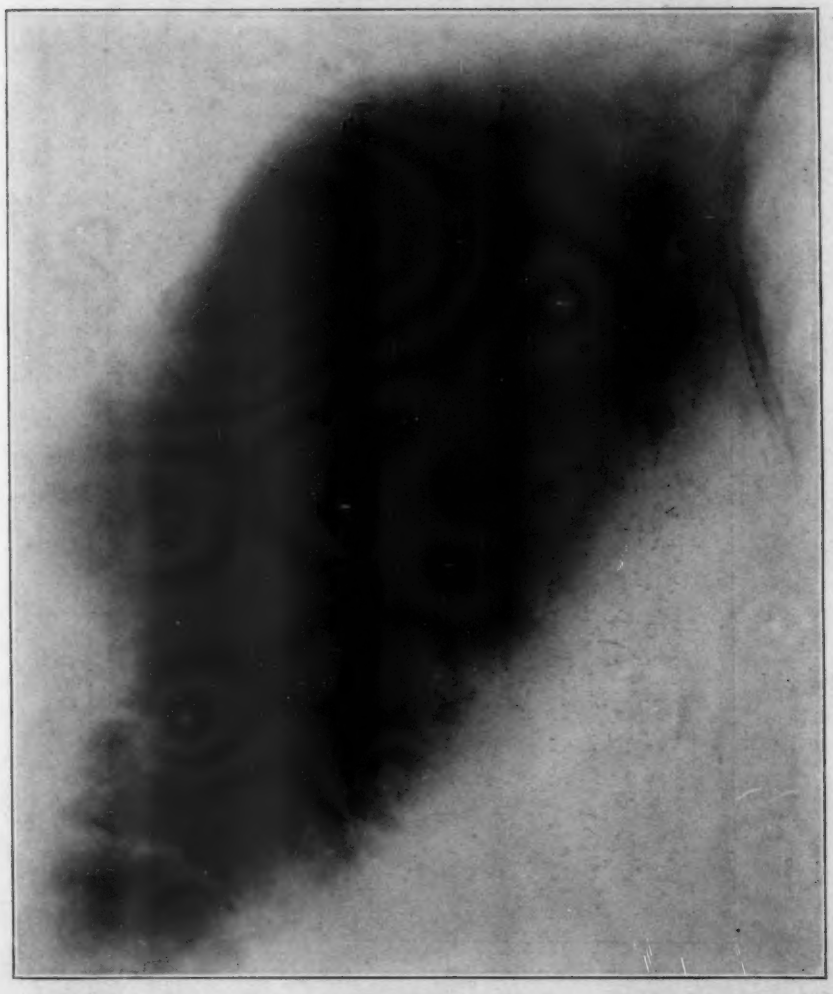

Fig. 7.—Appearance of tumor shown in Figures 4, 5 and 6 at late stage; entire length of humerus involved; dense compact bone in interior. If a tumor at this period of its growth is split in half the interior in many places will be found to consist of dense, compact bone completely enclosing cellular sarcomatous masses; these represent Nature's attempt at cure by locking off the malignancy.

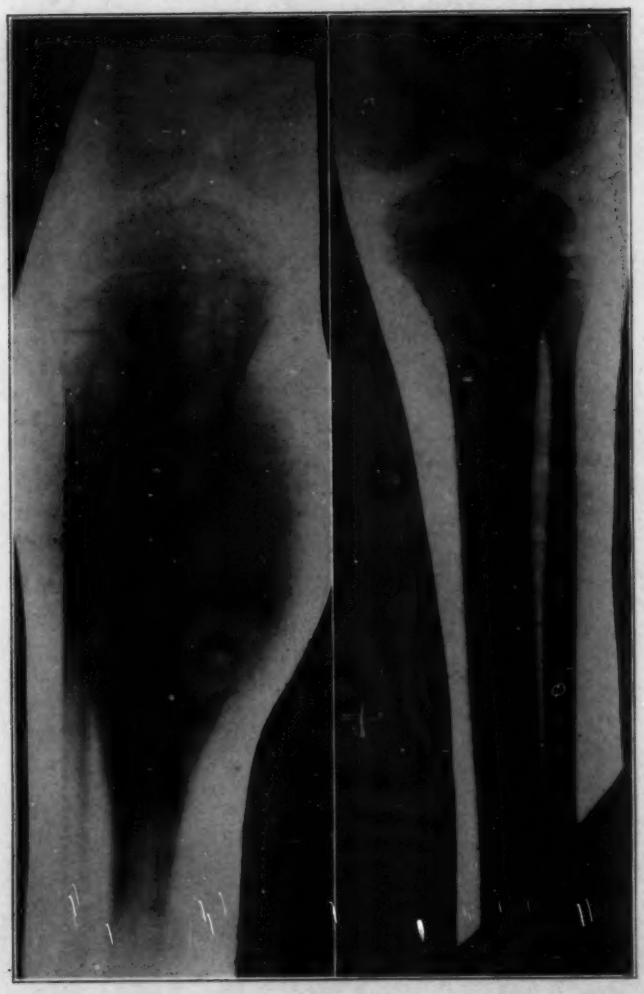

Fig. 8.—Early osteogenic sarcoma of tibia, showing periosteum raised to outer limits of the growth and vertical rays passing out from cortex; rays near cortex are more dense than at periphery and suggest inference that they originate in haversian canals and grow outward toward raised periosteum.

Fig. 9.—Vertical rays not due to sarcoma, in case of fibrous anchylosis of elbow after fracture (the fracture was operated on in Omaha four years before this roentgenogram was taken; metal pins are seen in picture).

Fig. 10.—Slow growing osteochondrosarcoma, which has been steadily growing larger for the last eight years, the patient persistently refusing amputation. As a general rule, the denser the new bone formation, the slower the growth and the less malignant the tumor.

Fig. 11.—Rapidly growing osteogenic sarcoma of the telangiectatic type, which produced very little bone but developed huge soft swelling involving entire shoulder, which was at first mistaken for a huge abscess; this tumor was rapidly fatal.

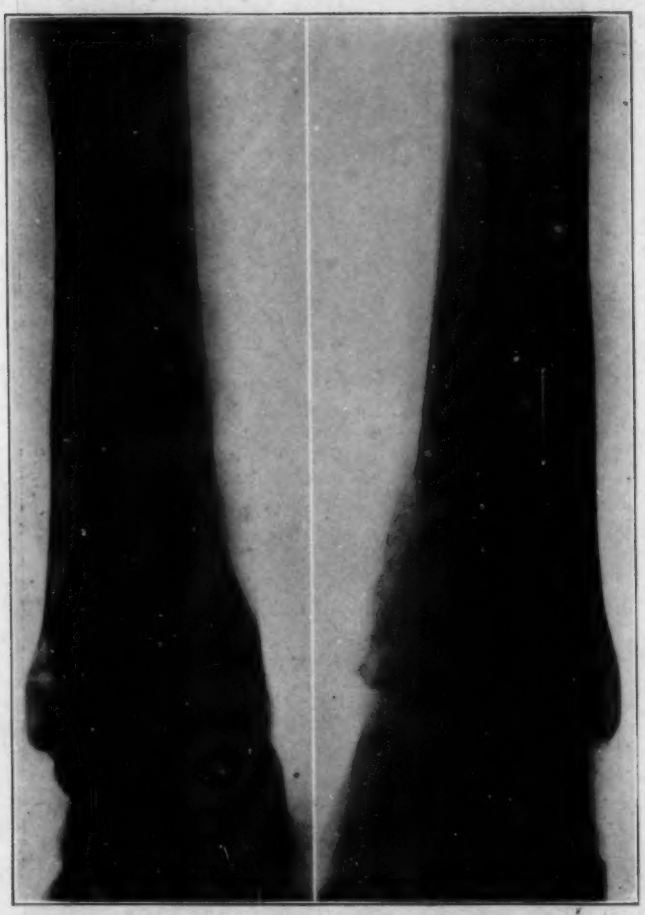

Fig. 12.—Osteolytic sarcoma (medullary type, occurring in cancellous tissue usually) in laborer, aged 30, following trauma; tumor was very vascular and involved soft structures extensively; local radical operation was soon followed by pulmonary metastases and death.

Figure 13

Figure 14

Fig. 13.—Ewing tumor or diffuse endothelioma in woman, aged 21, Sept. 22, 1924; patient had felt sudden pain in left thigh for three or four weeks; thigh was swollen and she walked with difficulty. She was put to bed and cautioned against fracture. Roentgen-ray and radium treatments were given.

Fig. 14.—Spontaneous fracture in thigh shown in Figure 13, which occurred while patient was in bed; a cast was applied, and roentgen-ray treatments were continued; these were followed by extensive bone regeneration.

Fig. 15.—Appearance of thigh of patient shown in Figures 13 and 14 when patient was walking with a brace; no metastases were observed.

INTERSTITIAL GROWTH IN GROWING LONG BONES *

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Growth of practically all the organs and tissues of the body takes place through a process of interstitial multiplication and increase in size of the individual cells that go to make up their structure. In order that these changes may take place, it is necessary that there be a plastic medium and sufficient space for expansion. An organ like the liver or a tissue-like muscle possesses such prerequisites, and they increase in size by interstitial growth. Even in a tissue of such firm consistency as cartilage, it is found that its increase in size is due to the multiplication and growth of the individual cells. This form of interstitial growth also takes place in the cartilaginous forerunner of bone, but it is questionable whether it occurs after the laying down of the lime salts and a completion of the transition into bone.

When the literature on the subject of interstitial growth was reviewed, it was found that there was considerable discrepancy in the results of different investigators and that, in some instances, erroneous interpretations and quotations had been made by other workers. Duhamel [1] noticed that bench marks on the stumps of trees maintained a constant level and that growth in the trunk did not change their relative position. He applied this method to the study of growing bone; he drilled holes into the shaft of growing bones at regular measured distances into which he inserted silver stylets to keep them open. After a definite period he killed the animal, measured the distance between the markers and found them unaltered, although there had been growth in length in the other part of the bone. He concluded that all growth in length must take place at the extremities of bones. In John Hunter's "Collected Works" [2] it is stated that Duhamel found some increase in growth in the middle portion of long bones but to a lesser degree than that which occurred at the extremities. Also, in the writings of Ollier [3] it is claimed that Duhamel got some separation of the implanted pegs in the cancellous bone of the extremities.

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* From the Surgical Laboratory of Stanford University School of Medicine.

1. Duhamel, H. L.: Sur les os Hist. Acad. roy. d. Sc. 1743 Anat. 1749 mem. **116**:153, 396. (Originals not available, quoted from Keith).

2. Hunter, John: Collected Works, IV, London, James F. Palmer, p. 317, 1837.

3. Ollier, Louis: Traité expérimental et clinique de la régénération des os étude la production artificielle due tissue osseux, Paris, **1**, 1867.

John Hunter [2] repeated Duhamel's experiment to ascertain if cylindrical bones are not elongated by new matter interposed in the interstices of the old. He bored two holes in the tibia of a pig, one near the upper end, and the other near the lower, the space between the holes being exactly 2 inches (5 cm.): a small leaden shot was inserted into each hole. When the bone had increased in length by the growth of the animal, the pig was killed, and the space between the two holes was found to be exactly 2 inches (5 cm.). The editor of Hunter's "Collected Works" calls attention to an apparent discrepancy in Hunter's findings and his conclusions. In a footnote he makes the following statements:

> It is not easy to understand how the unqualified assertion came to be published since the preparation and record confirmatory of those made by Duhamel are still preserved in the Hunterian Museum. The preparation (No. 188, Physiological Series) is the left tarsometatarsal bone of common fowl exhibiting two perforations at equal distances, two thirds of an inch (2.5 cm.) from the extremities of the bone. The original record of the experiment is preserved with the specimen.
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> The two extreme lines are the present length of the bone from the head to the joint of the inner toe. The two inner lines are the length when cauterized. The two outer dots are the present distances of the holes cauterized. The two inner dots are the distances of these holes when cauterized, so that the bone between the two holes has grown about two eighths of an inch, while the other parts have grown half an inch (Physiological Catalogue **1**:40).

Keith [4] also has called attention to this apparent discrepancy in Hunter's findings and his conclusions. Keith presents an entirely different view and explanation of the facts. He says:

> Hunter repeated Duhamel's experiments to prove that a bone could grow in length only at its extremities. He inserted two pellets into the tibia of a young pig. When the pig was full grown the pellets remained exactly the same distance apart. He also showed the shank bones tarsometatarso of fowls in which he performed similar experiments. One of the specimens is laid open and reveals the two pellets in the medullary cavity, the distance apart being the same as when implanted at the early stage in the growth of the bird. The other shows two canals leading into the medullary cavity. Bristles inserted into the canals show that both were inclined toward the upper or proximal end where is situated the main epiphyseal line of growth. Now when Hunter made the holes the bone was 71 mm. long and the distance between the two holes 42 mm.; when the fowl was killed, the bone was 91 mm. long, the distance between the holes 48 mm. At first sight it looks as though Hunter has proven that there has been an interstitial elongation of the shaft for the two holes have separated 6 mm. in the course of growth. Hunter has left no interpretation but I suspect that he had fathomed the matter, and realized that he had discovered the cause of the obliquity of the nutrient canals of long bone. The periosteum is firmly fixed to the epiphyseal line at the upper end of the metatarsal shaft where all the length in growth takes place. Note: The epiphy-

4. Keith, Arthur: Bone Growth and Bone Repair, Brit. J. Surg. **5**:685 (April) 1918.

ses of the metatarsal bones are at the lower or distal end.) That growth causes a drag on the periosteum, a drag which decreases in degree as the distal end of bone is approached. Hence the cauterized holes in the periosteum are dragged during the growth of the shaft in unequal degree toward the upper or growing end of the bone and thus become separated to an increased extent. Sixty years after Hunter's death, Sir George Humphrey explained the oblique course of the nutrient canals of long bones in the exact manner as shown by Hunter's experiment.

This explanation of Keith's may be correct but it is not clear just why the cauterized holes remained patent, as one generally finds that a hole bored in bone becomes filled with new bone. Even if the hole remains open the mechanics seem to be more complex than a simple unequal pull of the periosteum.

Flourens,[5] in his experiments, found that the spread at the extreme ends of the bone was due to deposits of new layers of bone at the epiphyseal cartilage plate between the diaphysis and epiphysis. He also found that nails implanted in the diaphysis never spread apart.

Ollier [3] evidently was not satisfied with the experiments made by the previous investigators, as he made some independent experiments along the same line. He found that small pegs implanted in the spongy part of the diaphysis, nearer the cartilage than in other experiments, in young chickens in some cases showed a separation of from 0.5 to 1.5 mm., and said that this would tend to prove what Duhamel believed, namely, that if pegs were placed in bones that were not completely hardened there would be a separation of the pegs. Because this separation is so slight and is not constant, Ollier stated that we should not utilize this little difference to alter the law of the non-elongation of bone tissue.

Macewen [6] invoked the law of interstitial growth to strengthen his contention that periosteum was not osteogenic. He said:

> Bone is living, and as every living tissue requires renewal, absorption and repair must be constantly recurring processes throughout life. These can only be carried out by interstitial changes. . . . The conditions for expansion prevail, space is provided for the proliferation of the osteoblasts which form interstitial growth in the interior of the shaft and may expand the bone peripherally.

He also says:

> Though the bone cell in its mature state is surrounded by calcareous walls, it is not imprisoned thereby, each cell controlling its immediate area. The inherent power of the bone cell calls forth the calcareous depositions within the area of its influence and retains the power of dispersing it.

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5. Flourens, J. P. M.: Recherches sur le development des os et des dent, Paris, 1842 (quoted from Ollier).

6. Macewen, William: The Growth of Bone, Glasgow, James Maclehose and Sons, 1912.

Another statement, without definite proof, summarizing his views is that:

Interstitial growth occurs in the diaphysis of long bones, contributing slightly to increase in length and markedly to circumferential augmentation.

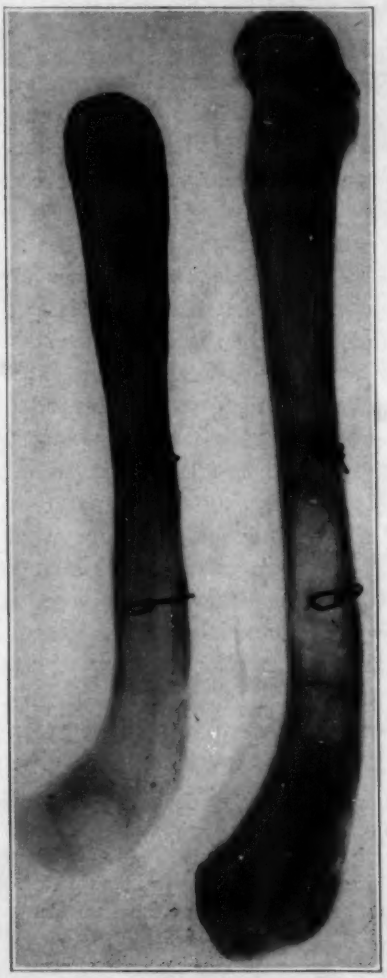

Fig. 1 (Experiment 8).—Roentgenograms taken at the time of operation and eighty-four days later. The relative position of the wires and the distance between them has not changed.

The concensus of opinion of the various investigators tends to sustain the idea that there is a limited amount of interstitial growth which produces a lengthening of long bones. No cognizance of these facts is taken in the teaching of today in which the entire longitudinal growth is ascribed to that which occurs at the epiphyseal cartilage plate.

Because of its scientific interest and on account of its bearing on certain problems concerning bone growth, it was thought to be of sufficient importance to warrant further study. With a preconceived idea that there might be a limited amount of linear growth independent of that which takes place at the epiphyseal cartilage plate, the following experiments were performed.

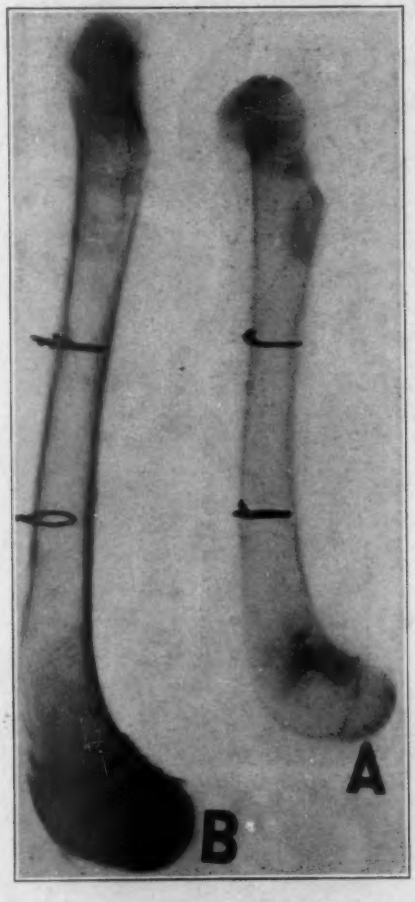

Fig. 2 (Experiment 9).—The roentgenograms taken at the time of operation and ninety-nine days later show no growth in length between the wires. In *B* is shown that there has been length growth both proximal and distal to the wires.

The operations were done on young dogs and rabbits under a general anesthetic with the usual aseptic technic. In the ten experiments on dogs, the femur was utilized and a silver wire or a nail was inserted as a marker. In ten experiments on rabbits either the metacarpal or metatarsal bone was used and small silver pellets inserted into the holes

were used as markers. The distances were measured and checked with a roentgenogram taken at a long constant target-film distance.

EXPERIMENTS ON DOGS

EXPERIMENT 1.—*Operation.*—In Dog 57 the left femur was exposed, and three wires were passed through the diaphysis at different places. The distance between the outer wires was 1.7 cm. The diameter of the bone was 0.65 cm. The animal died seventeen days after the operation.

Fig. 3 (Experiment 10).—Left, position of nails at time of operation; right, 166 days later. There had been no change in the position and no growth between them during that time, although there had been growth both proximal and distal to them.

Result.—There was good healing. The distance between the outer wires was 1.65 cm., and the diameter was 0.6 cm. Thus there had been no growth in length or thickness.

EXPERIMENT 2.—*Operation.*—In Dog 56 two wires were placed through the diaphysis of the right femur 1.9 cm. apart. The diameter of the bone was 0.75 cm. The animal died of pneumonia at the end of twenty days.

Result.—The distance between the wires was 1.9 cm., and the diameter was 0.75 cm. This showed that there had been no growth between the wires.

EXPERIMENT 3.—*Operation.*—In Dog 53 two wires were placed on the right femur 1.5 cm. apart. The diameter of the bone was 0.6 cm. The animal died in twenty-two days.

Result.—The distance between the wires was 1.45 cm., and the diameter was 0.65 cm. There was no growth between the wires.

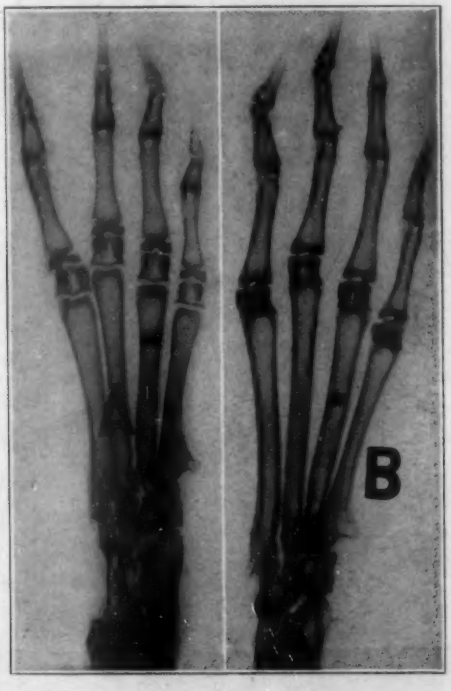

Fig. 4 (Experiment 11).—*A*, position of markers at time they were inserted; *B*, their position at end of experiment, 160 days later. There had been absolutely no change in their relative position or the distance between the silver pellets. In *B* it will be seen that there had been length growth distal to the markers.

EXPERIMENT 4.—*Operation.*—In Dog 58 two holes were bored through the diaphysis of the right femur 1.65 cm. apart, and wires were passed through each of these holes. The diameter of the bone was 0.7 cm.

Result.—At the end of twenty-eight days, the distance between the wires was 1.65 cm., and the diameter was 0.7 cm. This showed that there had been no growth.

EXPERIMENT 5.—*Operation.*—In Dog 55 two wires were passed through the diaphysis of the right femur 1.3 cm. apart. The diameter of the bone was 0.6 cm.

Result.—At the end of twenty-nine days, the distance between the wires was 1.3 cm., and the diameter of the bone was 0.6 cm.

EXPERIMENT 6.—*Operation.*—In Dog 47 two wires were passed through the diaphysis of the right femur 3.1 cm. apart.

Result.—At the end of thirty-two days, the distance from wire to wire was 3.1 cm., and there had been no growth between them during the period of observation.

EXPERIMENT 7.—*Operation.*—Four wires were passed through the diaphysis of the right femur. The distance between the outer wires was 3.1 cm. and between the inner was 1.1 cm.

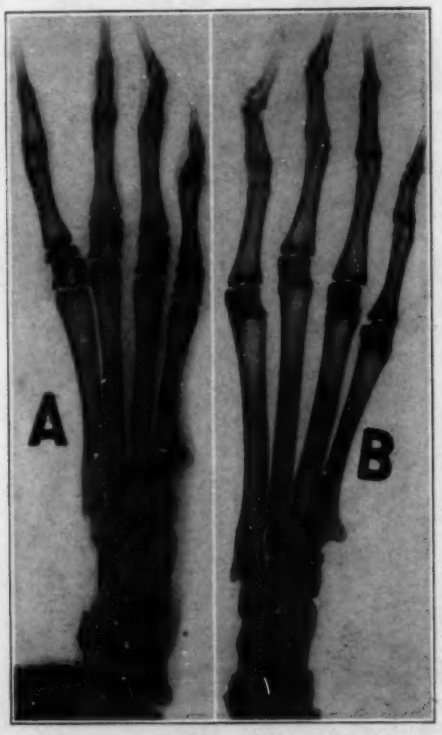

Fig. 5 (Experiment 12).—*A*, position of pellets when implanted; *B*, 159 days later. There had been no growth between the markers, but the bone distal to them had increased in length.

Result.—At the end of sixty-one days, the distance between the respective wires was 3.1 cm. and 1.1 cm., indicating that there had been no growth during the experimental period.

EXPERIMENT 8.—*Operation.*—In Dog 61 two wires were passed through the shaft of the right femur 2.1 cm. apart. The diameter of the bone was 0.9 cm.

Result.—At the end of eighty-four days, the distance between the two wires was 2.1 cm. The diameter of the bone was 1.1 cm. Thus there had been no growth in length between the two wires, but there had been an increase in thick-

ness of 0.2 cm. Figure 1 shows that the position of the wires had not changed. It was possible to superimpose the two films and have the position of each wire coincide.

EXPERIMENT 9.—*Operation.*—In Dog 59 two wires were passed through the diaphysis of the right femur 2.3 cm. apart. The diameter of the bone between the two segments of wire was 0.7 cm.

Result.—At the end of ninety-nine days, the distance betwen the two wires was 2.3 cm., while the diameter was 0.9 cm. Figure 2 shows the position of the wires at the time of operation and at the end of the experimental period. There was no change whatever, and it was possible to superimpose the two films to make the relative positions coincide.

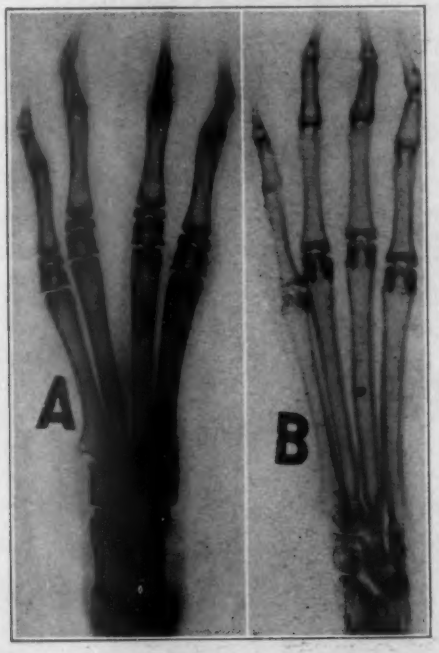

Fig. 6 (Experiment 13).—*A*, position of silver markers at time of operation; *B*, at the end of 159 days. There had been no growth between the shots.

EXPERIMENT 10.—*Operation.*—In Dog 54 two nails were driven into the shaft of the right femur 2.3 cm. apart. The diameter of the bone was 0.9 cm.

Result.—At the end of 166 days, the distance between the nails was 2.35 cm. The diameter of the bone was 1.15 cm. There was no increase in length between the two wires although the diameter had increased 0.25 cm. Figure 3 shows the position of the nails unchanged, although the remainder of the bone has increased in length. The film taken at the time of operation could be exactly superimposed to make the two nails exactly overlap each other.

In none of the ten experiments on dogs in which wires were passed through the diaphysis or nails implanted in the shaft was there any

change in the relative position of the wires or nails. Thus it may be concluded that there was no interstitial proliferation of the bone tissue between the two wires.

There was an increase in thickness of the shaft between the wires due to the deposit of new bone from the periosteum.

EXPERIMENTS ON RABBITS

In the experiments on rabbits small pellets of silver were implanted into the metatarsal bones. Particular attention was directed to their

Fig. 7 (Experiment 14).—*A*, position of pellets at time of operation; *B*, at end of experiment, 154 days later. There had been no change in the distance between the markers.

positions so that they would occupy different distances from the actively growing bone in the region of the epiphyseal cartilage plate. It would be expected that if there was any elongation it would be found in the young osteoid tissue of the metaphysis.

EXPERIMENT 11.—*Operation.*—In Rabbit 012 two small holes were cauterized in the cortex of the third metatarsal bone of the right foot. The distance between the holes was 1.7 cm. A small silver pellet was placed in each hole.

Result.—At the end of 160 days, the pellets were found almost entirely covered by new bone, and the distance between them was 1.75 cm. The roentgenogram shows that the position of the markers has remained unchanged (Fig. 4),

but that there has been an increase in length distal to the pellets. When the films were superimposed, the two shadows of the markers exactly coincided.

EXPERIMENT 12.—*Operation.*—In Rabbit 013 two pellets were buried in holes burnt in the cortex of the third right metatarsal bone at a distance of 1.5 cm. apart.

Result.—At the end of 159 days, the pellets were found buried in the bone, and there was no evidence of the burnt track. The distance between the two markers was 1.4 cm. The position of the markers remained unchanged and the

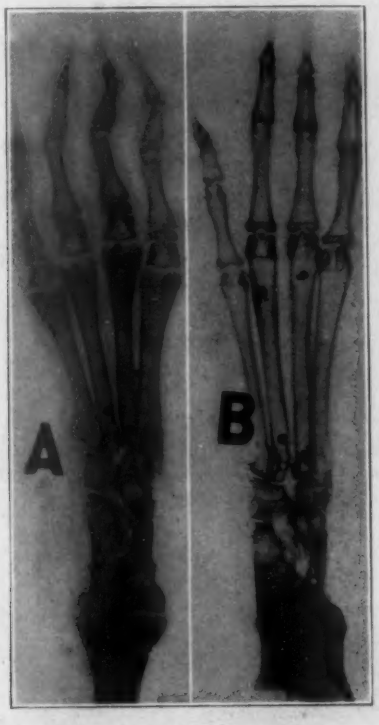

Fig. 8 (Experiments 15 and 16).—In these two experiments the distal markers have been inserted in the metaphysis near the epiphyseal cartilage plate, *A*. It would be expected that if there was any interstitial growth it would be found in the new osteoid tissue of the metaphysis. *B* shows the position of the markers unchanged at the end of 112 days. The original films when superimposed showed the two shadows of the pellets coinciding.

superimposed shadows exactly coincided in the films taken at the time of operation and at the conclusion of the experiment (Fig. 5).

EXPERIMENT 13.—*Operation.*—In Rabbit 015 the same procedure was carried out as in Experiment 12, and the distance between the pellets was 1.4 cm.

Result.—At the end of 159 days, the pellets were found buried in the bone 1.3 cm. apart. The shadows of the markers in the roentgenograms exactly coincided (Fig. 6). Thus there was no growth between the wires, although there had been an increase in length of the bone distal to the markers.

EXPERIMENT 14.—*Operation.*—In Rabbit 017 two holes were bored in the bone instead of being burned at distances of 1.7 cm.

Result.—At the end of 154 days, the two pellets were found buried in the bone and were 1.75 cm. apart. The roentgenograms (Fig. 7) showed that there had been no change in the position of the markers from the time they had been buried until the termination of the experiment.

EXPERIMENT 15.—*Operation.*—In the experiment on Rabbit 018, one of the holes was burnt in the metaphysis to determine if there would be any possibility of interstitial growth in the early formed bone. The distance between the implanted pellets was 1.9 cm.

Fig. 9 (Experiments 17 and 18.)—*A*, position of pellets when inserted at operation; *B*, their position at end of experiment, 112 days later. There has been no increase in the distance between the markers, although the bone distal to them has grown in length.

Result.—At the end of 112 days, the distal shot was still partially exposed, but the proximal one was buried in the bone. The distance between the markers was 1.95 cm. The roentgenograms show that there has been no change in the position and the shadows could be superimposed. There had been growth distal to the shots (Fig. 8).

EXPERIMENT 16.—*Operation.*—In Rabbit 018 the same method was employed as in Experiment 15 except that the distal marker was placed nearer to the epiphyseal cartilage plate. The distance between the pellets was 2.2 cm.

Result.—At the end of 112 days, the proximal shot was buried but the distal was still slightly exposed. The measured distance was 2.4 cm. The roentgenograms show that there had been no change and that the distance between the pellets was the same.

EXPERIMENT 17.—*Operation.*—In Rabbit 019 two holes were cauterized in the fourth right metartarsal bone, the distal one being well up in the metaphysis. Two silver markers were placed in each hole, which were 2.1 cm. apart.

Result.—At the end of 112 days, the proximal shot was found buried by bone while the distal was exposed. The measured distance was 2.4 cm., which

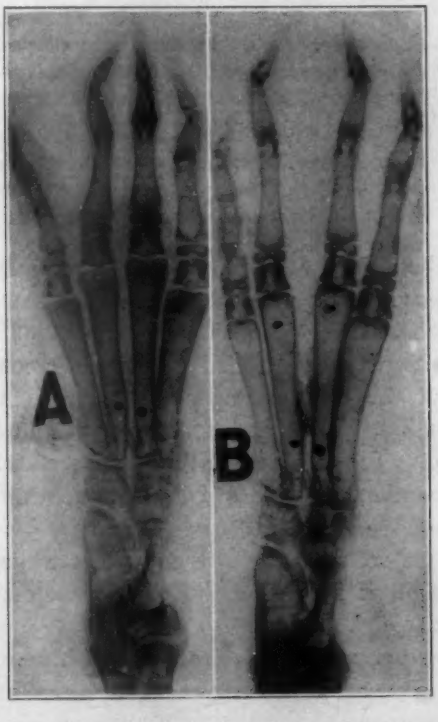

Fig. 10 (Experiments 19 and 20).—*A,* position of markers at time of operation; *B,* their position forty-three days later. There had been no change in the distance between the markers, although the distal part of the bone had increased in length.

was 0.3 cm. more than at the time of operation. If the two films are superimposed (Fig. 9) or the distance measured on the plate, it will be found that there has been no change in the position of the markers. The roentgenogram provides a much more accurate method and is free from the chance of error of measurements at operation.

EXPERIMENT 18.—*Operation.*—In Rabbit 019 a similar procedure was carried out on the third metatarsal bone except that the distal hole was placed a little nearer the epiphyseal cartilage plate. The measured distance between the markers was 2.1 cm.

Result.—At the end of 112 days, the proximal shot was buried but the distal was slightly exposed. The measured distance between the shorts was 2.25 cm. The roentgenograms show that there has been no change in the position of the markers (Fig. 9).

EXPERIMENT 19.—*Operation.*—In Rabbit 020 two holes were cauterized in the cortex of the fourth right metatarsal bone 1.6 cm. apart and filled with silver markers.

Result.—At the end of forty-three days, the proximal shot was buried but the distal was partially exposed. The measured distance between them was 1.65 cm. The roentgenograms showed no change in the position of the pellets (Fig. 10).

EXPERIMENT 20.—*Operation.*—In Rabbit 020 the same procedure was carried out as in Experiment 19 except that the distal marker was placed a little nearer the epiphyseal cartilage plate of the fourth metatarsal.

Result.—At the end of forty-three days, the distance between the pellets measured 1.9 cm., which was the same as at the time of operation. The roentgenogram showed that there was no change in the position of the markers, although the distal end of the bone had increased in length (Fig. 10).

In none of the rabbit experiments was there any change in the position of the markers or increase in the distance between them in growing bones.

All experiments were controlled by measurements taken on the roentgenograms at the time of the operation and at the end of the period of observation. With a constant target-film distance there is practically no chance for error, as is the case in making measurements at the time of operation. The record is permanent and can be checked as often as desired.

In no case was there a change in the angle at which the marker was implanted or any other indication that the periosteum exerted a pull toward the growing end.

All bored or cauterized holes were filled with new bone.

CONCLUSION

Interstitial proliferation of osseous tissue plays no part in the elongation of a growing bone, either in the mature bone or the young osteoid tissue bordering on the epiphyseal cartilage plate.

Length growth of bone is entirely dependent on the purposeful multiplication of the cartilage cells of the epiphyseal cartilage plate.

STRANGULATED HERNIA FROM THE STANDPOINT OF THE VIABILITY OF THE INTESTINAL CONTENTS

REPORT OF TWO HUNDRED AND SEVENTY-EIGHT CASES *

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In two cases of strangulated hernia in which the patients were operated on recently, the contents of the sac were thought viable and were therefore replaced within the abdomen. Subsequent necropsies revealed gangrene of these intestinal loops with a plastic peritonitis. In order to determine the frequency of this untoward complication a statistical review of all cases of strangulated hernia for a period of ten years was made. There were 4,139 patients with abdominal hernias admitted to the surgical wards of the Mt. Sinai Hospital from Jan. 1, 1914, to Dec. 31, 1923. Of this number 3,208 of the cases were inguinal, 294 femoral, 377 ventral, 167 umbilical, 85 epigastric, and 8 comprised the rarer varieties. The classification is given in Table 1. Of the total number 278, or 6.7 per cent., were strangulated. These all had the characteristic of strangulation in that there was a direct interference with the blood supply of the hernial contents. There were 142 inguinal, ninety-six femoral, twenty-six umbilical, twelve ventral, one epigastric and one properitoneal.

One hundred and fifty-nine of these hernias occurred in males, 119 in females, with the sex distribution in the different varieties as shown in Table 2. The ages in which strangulation occurred were variable. No age was exempt. The various decades with their mortality and percentages is recorded in Table 3. It is interesting to note that thirty occurred in the first decade. The reason that strangulation happens so frequently in children might be explained by the fact that these small hernias are often unrecognized and the crying of infants combined with their ceaseless activity often results in a sudden strangulation of the hernial contents. However, the majority occur from the fourth to the sixth decade. At this time of life there are several factors that might increase intra-abdominal pressure. In some cases there is a greater straining action in defecation and urination. In other patients, suffering

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* From the surgical service of Dr. A. V. Moschcowitz, Mt. Sinai Hospital. Read in abstract before the surgical section, New York Academy of Medicine, May 4, 1925.

TABLE 1.—*Classification of Four Thousand One Hundred Thirty-Nine Hernias (1914-1923)*

	Cases	Per Cent.	Cases	Per Cent.
Inguinal hernia			3,208	77
Inguinal, direct and indirect	2,886	90		
Inguinal, strangulated	142	4		
Inguinal, recurrent	180	5		
Femoral hernia			294	7
Femoral	194	66		
Femoral, strangulated	96	32		
Femoral, recurrent	4	1		
Ventral hernia			377	9
Ventral	356	94		
Ventral, strangulated	12	3		
Ventral, recurrent	9	2		
Umbilical hernia			167	4
Umbilical	138	83		
Umbilical, strangulated	26	15		
Umbilical, recurrent	3	1		
Epigastric hernia			85	2
Epigastric	84	99		
Epigastric, strangulated	1	1		
Other varieties of hernia			8	1

TABLE 2.—*Sex Distribution*

Type of Hernia	Sex	
	Male	Female
Inguinal	130	12
Femoral	20	76
Umbilical	5	21
Ventral	3	9
Epigastric	1	0
Properitoneal	0	1
	159	119

TABLE 3.—*Age at Which Strangulation Occurred*

Age	Inguinal	Died	Femoral	Died	Umbilical	Died	Ventral	Died	Properitoneal	Died
1 to 10 years	27	3	1	0	2	1	0	0	0	0
11 to 20 years	8	0	2	0	0	0	0	0	0	0
21 to 30 years	12	1	4	0	2	1	1	0	0	0
31 to 40 years	13	0	15	1	4	0	2	0	0	0
41 to 50 years	11	3	30	3	4	1	5	0	1	0
51 to 60 years	20	3	15	4	9	2	3	0	0	0
61 to 70 years	24	2	22	3	5	2	0	0	0	0
71 to 80 years	18	2	5	3	0	0	0	0	0	0
81 to 90 years	4	1	1	1	0	0	0	0	0	0
Not mentioned	3	0	3	0	0	0	1	0	0	0

Summary of All Hernias

Age	Total Number of Hernias	Died	Mortality, per Cent.
1 to 10 years	30	4	13
11 to 20 years	10	0	0
21 to 30 years	18	2	11
31 to 40 years	34	1	3
41 to 50 years	51	7	14
51 to 60 years	47	9	19
61 to 70 years	51	7	14
71 to 80 years	23	5	22
81 to 90 years	5	2	40
Not mentioned	6	0	0

from emphysema, there are apt to be sudden spells of coughing, and in some subjects, especially women, there may be an increased deposition of fat in the peritoneal cavity.

The length of time that a patient has a hernia bears no relationship to the incidence of strangulation. For strangulation may occur primarily, as it did in forty-four cases, or secondarily to a hernia that has been existent more than thirty-five years. As a rule, however, the larger inguinal hernias are not apt to strangulate as frequently as the smaller ones, because the external ring in the former is usually more relaxed. In cases of femoral hernia in which the crural canal is small and narrow, strangulation occurs relatively more often than in the other varieties. Strangulation in the ventral group, in which the ring as a rule is large and relaxed, is rare.

The exciting element that precipitates strangulation cannot always be traced. It usually follows some straining action occurring during exercise, work, coughing, defecation or urination. In others it seemingly follows complete relaxation, such as would be obtained while taking a warm tub bath.

The symptoms presented are definite and almost stereotyped. The pain is sudden in onset, sharp in character and localized to the region of the hernia where a mass is invariably noticed. This local pain is soon followed by generalized abdominal pain, cramplike in nature, coming on in spasms. In some cases, especially in the femoral group, the pain may be general in nature, localizing to the groin only later. These are the cases in which an exploratory laparotomy is occasionally performed for intestinal obstruction, the operator not realizing that the source of the obstruction is intestine caught in a hernial sac. Nausea followed by vomiting was present in more than 60 per cent. of the cases, occurring in more than 77 per cent. of the femoral hernias and in more than 50 per cent. of the inguinal hernias. The frequency, amount and character of the vomitus depend on the type and degree of obstruction of the contents of the sac. When there has been complete obstruction for more than twenty-four hours there may be vomiting of small intestinal contents and with it the general prostration and collapse which, as a rule, accompanies all cases of acute intestinal obstruction. This was observed in ten cases. Obstipation was present in over 50 per cent. of the cases.

The pulse in the early hours of strangulation is slow, increasing only after the first twelve hours have passed. The temperature is normal or subnormal. Elevation of temperature is very uncommon, and if present means that some complication has intervened, either gangrene, peritonitis, local infection or pneumonia. The physical examination of the region of the hernia discloses a firm, tense, elastic, irreducible mass, excruciatingly tender to palpation or to pressure, especially in the region

of the neck of the sac. Loss of tenderness to pressure is of diagnostic importance because it invariably means gangrene of the contents. The overlying skin, as a rule, is normal in color. In only ten cases did it share in the inflammation of the underlying contents. As a rule, the integument is freely movable, but the mass beneath is firmly attached to the deeper parts and there is no impulse on coughing. The size of the hernial tumor varies greatly, depending on its contents and location. In inguinal hernia, the mass may be small and rounded, barely palpable in the region of the internal ring; it may be oblong, occupying the inguinal canal, or it may be so large that it fills the greater part of the scrotum or the labia. The mass in femoral hernia usually is smaller in size, ovoid and tender. In fact, in a hurried examination, it may easily be overlooked. In the early stages, the abdomen is usually soft and lax. Later, when intestinal obstruction occurs or peritonitis intervenes, it may become distended or rigid. Distention occurred in twenty-five cases and six gave evidence of visible peristalsis.

TABLE 4.—*Anesthesia and Mortality in Strangulated Hernias*

Type of Anesthesia	Inguinal	Living	Died	Femoral	Living	Died	Umbilical	Living	Died	Ventral	Living	Died
Local	51	43	8	51	43	8	8	6	2	4	4	0
Gas and ether	48	42	6	40	35	5	12	9	3	6	6	0
Gas and oxygen	7	7	0	8	7	1	3	2	1	2	2	0
Ether	24	23	1	0	0	0	2	2	0	0	0	0

Summary

Anesthesia	Total Number	Died	Mortality per Cent.
Local	114	18	15
Gas and ether	106	14	13
Gas and oxygen	20	2	10
Ether	26	1	4

152 cases; 27 died; 17 per cent.

The diagnosis of strangulation is the indication for immediate operation. A moribund patient is the only contraindication. Attempts to reduce the mass by taxis so that an operation may be avoided is an inheritance from the days of preaseptic surgery. It is a very dangerous, blind and unsatisfactory procedure. In this series there were two cases in which taxis had been performed and the hernial contents reduced with the result that the intestines subsequently became gangrenous and the patients died. If taxis must be used, it should be employed only in those cases which are very recent in their inception and, if after a few minutes of very gentle manipulation, the mass is still irreducible, no time should be lost in proceeding immediately with an open operation.

The choice of an anesthetic is very important. A glance at Table 4 would make it appear that the mortality with general anesthesia is no greater than with local. This is a wrong deduction. Local anesthesia is employed as a rule in cases in which the patients are so ill that a general anesthetic could never be administered. If local anesthesia is

the method of choice in the dangerously sick, why should it not be used in a routine manner in all these cases? It is granted that a better and quicker hernioplasty may be performed under general anesthesia, but the primary object of this operation is to save the patient's life. In the final analysis, what these patients are suffering from is an acute intestinal obstruction. They have been injured more or less by the absorption of intestinal toxins and the added poison of an inhalation anesthetic might be sufficient to cause death. The average patient with strangulated hernia will tolerate local anesthesia better than the patient with the interval type. The tissues in the immediate vicinity of the sac are inflamed and infiltrated from congestion and pressure. This edema seems to reduce the sensitiveness of the tissues to pain so much that after the primary anesthetization of the skin the operation may be performed quite painlessly with little or no additional procain infiltration. There are, however, children and others temperamentally so

TABLE 5.—*Duration of Strangulation and Mortality*

Hours of Strangulation	Inguinal	Living	Died	Femoral	Living	Died	Umbilical	Living	Died	Ventral	Living	Died
1 to 12	62	57	5	22	20	2	6	6	0	5	5	0
13 to 24	27	24	3	21	20	1	6	4	2	2	2	0
25 to 48	19	15	4	15	12	3	3	1	2	0	0	0
49 to 72	11	9	2	20	12	8	2	0	2	1	1	0
73 or over	14	12	2	11	10	1	8	7	1	3	3	0
Not stated	..	..	..	5	4	1	..	..	..	..	..	..

Summary of All Strangulated Hernias

Hours Strangulated	Total Number	Living	Died	Mortality, per Cent.
1 to 12	95	88	7	6
13 to 24	56	50	6	10
25 to 48	37	28	9	24
49 to 72	34	22	12	34
72 or over	30	33	3	8

constituted that inhalation anesthesia must be resorted to. If this is the case, gas and oxygen is probably the anesthetic of choice, excepting in infants, in whom open drop ether is much safer. The dangers of aspiration pneumonia in cases of intestinal obstruction, while greatly exaggerated, are always potentially present and before the administration of a general anesthetic it is always advisable to lavage the stomach.

In Table 5 showing the length of time of strangulation and morbidity, the importance of early operation is forcibly emphasized. There was a mortality of about 6 per cent. in those patients suffering from strangulation less than twelve hours; this gradually and progressively increased to a mortality of 34 per cent. in those obstructed between forty-nine and seventy-two hours. After the third day the mortality dropped to 8 per cent. This is to be expected. Any patient surviving four days has a fair prognosis, because it is safe to assume that either there must be an incomplete obstruction or, what is more likely, that the contents of the sac are omental and not intestinal. It should always

be remembered, however, that gangrene of hernial contents, especially in the femoral variety, may occur quite early, even within the first twelve hours.

The operative procedure is practically the same as in the interval hernia, except that the strangulated contents of the sac must be examined carefully before being replaced in the abdominal cavity. It is always better to open the sac before the constricting element is divided. This precaution will prevent the contents from slipping back into the peritoneal cavity before their pathologic condition has been adequately determined. This is not always practical. In inguinal hernia, in which the constriction is caused by the external ring, the fascia of the external oblique is usually divided before the sac is opened.

The constricting tissue causing the strangulation should always be divided under guidance of the eye and from within outward, rather than from without inward. The hernia knife and a grooved director are invaluable instruments for this procedure. In femoral hernias, the constricting element is usually the falciform margin of Gimbernat's ligament. While this may be divided inferiorly, it is a better and safer procedure to divide it from its abdominal side, because injury to the aberrant obdurator artery is less likely. It should not be inferred that this vessel is commonly present in strangulated femoral hernias. Its existence, however, is not an anatomic myth. Its surgical importance is more fully respected when it has been divided inadvertently, resulting in annoying and often alarming hemorrhage. By exposing Gimbernat's ligament from its abdominal side, not only can the obdurator artery be clearly seen, but an excellent exposure is also obtained of the peritoneal diverticulum as it enters the crural canal, the iliac vessels and the bladder. In opening any edematous sac, great care should be taken to avoid opening the last named structure.

As the sac is incised, fluid invariably escapes, and the character of the fluid is an index of the severity of the pathologic process. In the early stages of congestion of the hernial contents the fluid is clear, lemon yellow and odorless. Later, it may contain flakes of fibrin. When the stage of congestion passes into that of inflammation, the fluid may become blood-tinged to bloody, and when there is a sickening, cadaveric odor, gangrene is invariably present. In a case not included in this series in which the patient was operated on recently, the color of the fluid was a pinkish amber, yet a peculiar fecal odor was present. The intestine, which appeared clinically viable, was replaced and subsequent necropsy revealed gangrene of the intestinal wall with a plastic peritonitis. It is an open question whether a fecal odor to the fluid should not prejudice one strongly in favor of a resection.

Occasionally at operation the sac was found empty although before operation it had contents. This happened six times in this series. It

may be accounted for by the automatic reduction in recent strangulation induced by a relaxation of the constricting tissues obtained by general anesthesia. The contents of the hernial sac are not without interest and are enumerated in Table 6. The small intestine was by far the most common. Omentum was not infrequent. The mortality in those cases which contained both intestine and omentum was 9 per cent., in contradistinction to those which contained intestine alone, in which the mortal-

TABLE 6.—*Contents of Sac*

Sac Contents	Inguinal	Died	Femoral	Died	Umbilical	Died	Ventral	Died	Epigastric	Properitoneal
Intestine	82	12	49	11	9	5	2	0	1	1
Omentum	13	1	13	1	10	1	1	1	1	1
Intestine and omentum	16	2	17	2	5	0	7	0	..	..
Transverse colon	4	0	0	0	0	0	2	0	..	..
Appendix and cecum	5	0	0	0	1	0	0	0	..	..
Sigmoid	7	0	0	0	0	0	0	0	..	1
Epiploic appendix	1	0	2	0	0	0	0	0	..	..
Empty sac	8	0	5	0	0	0	0	0	..	..
Testis	6	0	0	0	0	0	0	0	..	..
Bladder	4	0	0	0	0	0	0	0	..	..
Cases not stated	6	0	6	0	1	0	0	0	..	..
Patients not operated on	7	0	1	0	0	0	0	0	..	..

Summary

Sac Contents	Total Number	Died	Mortality, per Cent.
Intestine	142	28	19
Omentum	37	3	9
Intestine and omentum	45	4	9

TABLE 7.—*Mortality Statistics According to Pathology of Strangulated Hernia Contents*

Hernia	Stage of Congestion	Lived	Died	Stage of Inflammation	Lived	Died	Stage of Gangrene*	Lived	Died
Inguinal	106	101	5	23	15	8	4	2	2
Femoral	61	58	3	17	13	4	17	10	7
Umbilical	22	17	5	3	1	2	1	1	0
Ventral	8	8	0	4	4	0	0	0	0
Epigastric	1	1	0	0	0	0	0	0	0
Properitoneal	1	1	0	0	0	0	0	0	0
Total	199	186	13	47	33	14	22	13	9

Summary

Mortality in stage of congestion	6.5 per cent.
Mortality in stage of inflammation	29 per cent.
Mortality in stage of gangrene	40 per cent.

* An intestinal resection was performed in these cases.

ity was 19 per cent. The omentum probably took the greater part of the constricting strain and, as is usual, acted as a capable protector for the bowels.

The viability of the hernial contents is of immediate and prime importance. There are three possibilities presented in any strangulation: either the contents are unquestionably viable, or they are definitely not viable, or their viability is doubtful. The first impressions of the hernial contents are deceptive, for their appearance when the sac is opened is of

little importance. The majority of contents are extremely congested, but when the constriction is relieved their circulation is reestablished within a short time. The pathologic appearance of the strangulated contents may clinically be divided roughly into three classes (Table 7), those in which congestion is present, those in which there is inflammation and, finally, those in which there is frank gangrene. In the first group after the constriction has been relieved and hot saline applications applied, the normal color usually returns. The serosa is smooth, glistening and shiny, peristalsis is present and pulsations are felt in the radicals of the mesenteric vessels. Viability in this group is assured invariably and there is no hesitancy in replacing the contents. In 186 cases falling into the stage of congestion the mortality was 6.5 per cent. The indication is clear in those cases in which there is definite and frank gangrene. If, however, the serosa is dull, the hue of the intestine dark, peristalsis sluggish and pulsation in the vessels weak, viability is unquestionable. It is these doubtful cases that tax the surgical judgment of the average operator. The ability of nature to resurrect the viability of the average damaged intestine has probably been exaggerated. In this series there were sixty-nine cases in which the compromised intestine had passed beyond the stage of congestion. Twenty-two of these were definitely gangrenous and resection was performed. In forty-seven, after due deliberation, the contents were thought viable and were therefore reduced. Fourteen, or 30 per cent., of these patients subsequently died, the clinical picture in many of them resembling either intestinal obstruction, peritonitis or both. This, to repeat, is only the clinical cause of death.

Unfortunately, only ten of these cases were checked by a postmortem examination; their histories, operative findings, postoperative course and necropsy results are given here.

REPORT OF CASES

CASE 1.—A man, aged 21, was admitted, July 2, 1919, to the service of Dr. Edwin Beer, and died the same day. The diagnosis was strangulated, right inguinal hernia. There was hemorrhagic infarction of the ileum and bronchopneumonia. Hernioplasty for strangulated, right inguinal hernia was done.

For the last three days, there had been pain in the abdomen, cramplike in character and recurring at frequent intervals. For two days he had had hiccups, which were very distressing, and he had frequently vomited dark colored material.

Physical examination showed a well nourished man, acutely ill. General physical examination was negative. The abdomen was very much distended and tympanitic. There was an indefinitely tender mass over the entire abdomen, but no rigidity. In the right inguinal region, a hard, tender and irreducible mass was present.

A right inguinal incision was made. There was about 3 inches (7.6 cm.) of small intestine in the sac, dark blue with some fibrinous exudate on the surface of the serosa. There was a large amount of free fluid in the abdomen. The

sac was freed, and the contents were reduced by typical Ferguson Andrew's hernioplasty. During anesthesia, the patient vomited a large amount of brownish fluid. A stomach tube was passed and more fluid was evacuated.

At 4:30 p. m., the patient became cyanotic, and the pulse was rapid and weak; he was given stimulation. At 5:45, the condition was worse; cyanosis was more marked, the pulse imperceptible. He died.

Necropsy revealed the abdominal cavity filled with 50 c.c. of blood tinged fluid. The intestine was normal except a small area 6 inches (15.2 cm.) from the ileocecal valve which was intensely congested and discolored. Its walls were edematous and distinctly thinned. There was a slight amount of bloody exudate in the lumen at the area of infarction, which was about 3 inches (7.6 cm.) in length. The peritoneum covering the portion of intestine was dull in appearance, markedly injected and covered with a small amount of fibrinous exudate. The heart was normal. In the right base of the lungs, there was marked congestion and infiltration.

CASE 2.—W. W., a woman, aged 63, whose mother was born in Austria, was admitted, Dec. 9, 1922, to the service of Dr. A. A. Berg and died, December 12. The diagnosis was strangulated, umbilical hernia, with gangrene of the small intestine. A Mayo hernioplasty for umbilical hernia was performed.

The patient had had an umbilical hernia for twenty-two years which on occasions would become irreducible. The condition was usually relieved by taxis or by elevation of the foot of the bed and enemas. Twelve hours before admission a mass appeared in the region of the umbilicus which was irreducible and painful. There was no nausea or vomiting. The patient had been constipated for the last forty-eight hours.

Physical examination revealed temperature, pulse and respiration normal. The patient was in acute pain. In the midline of the abdomen just above the umbilicus was a rounded mass, measuring 15 cm. transversely and 10 cm. vertically. This mass was firm and flat on percussion and the skin over it was not red. The abdomen was soft and lax; in the left inguinal region there was a hernia. Otherwise, the physical examination was negative.

An operation was performed the day of admission under local anesthesia. The sac contained a loop of strangulated intestine and omentum with a moderate amount of free sanguineous fluid. There were very dense adhesions binding the contents to the sac. When the tension at the neck of the sac was relieved, the intestine regained its normal color and peristalsis. The intestine was replaced, but the strangulated omentum was resected. A typical Mayo hernioplasty was then performed.

December 10, there was marked distention. The patient vomited coffee ground material and hiccuped persistently. Examination of the chest showed the presence of coarse râles over both lungs anteriorly and posteriorly.

December 11, the patient was vomiting large amounts of brown fluid. The condition gradually grew worse and the patient died.

When the abdominal cavity was opened at necropsy, a mass of omentum the size of a large orange was brought to view. It was edematous, congested, hemorrhagic and partly gangrenous. A hemorrhagic, gangrenous loop of jejunum about 10 cm. long which was not adherent to any other structure was also brought to view. That portion of small intestine which lies proximal to the gangrenous loop was greatly dilated and contained fecal fluid. The remainder of the small intestine was collapsed. There was no peritonitis. There was present a left inguinal hernia and the hernial sac contained several loops of small intestine bound by fibrinous adhesions. The other organs showed no definite changes beyond those of old age.

CASE 3.—K. B., a man, aged 60, whose mother was born in Turkey, was admitted, Jan. 24, 1922, to the service of Dr. H. Lilienthal and died, January 31. The diagnosis was strangulated, indirect, left inguinal hernia, with gangrene of the small intestine. An exploratory laparotomy was performed, which was followed by distention and vomiting. Jejunostomy was then done.

The patient had had a hernia for two years. On the day of admission, the mass suddenly became painful, irreducible and increased greatly in size. He vomited twice, the vomitus containing coffee ground material. On admission, the hernia was easily reduced by the house surgeon, but two hours later the patient complained of abdominal pain and the passage of blood by rectum. Before operation there were three bowel movements, each containing fresh and clotted blood.

Physical examination revealed a man of about 60, acutely ill. The temperature was 99.8; pulse, 80, and respiration, 24. Examination was negative except for a slightly distended abdomen. When he coughed, there was an impulse palpable at the left ring.

An operation was performed, Jan. 24, 1922, and a large quantity of blood was found in the peritoneal cavity. The descending colon was bluish and contained blood. Two feet (60.9 cm.) of bowel were sharply demarcated, firm and infiltrated with blood. The serosa was not glistening. It was missing in some places and shaggy in others. The loops were beefy red without any normal patches of intestine. There were hemorrhages into the mesentery especially marked toward the root. Pulsations were neither seen nor felt, but there were traces of peristalsis in the involved loops.

Under ether anesthesia, a lower four inch (10.1 cm.), right rectus incision was made. The intestine was carefully examined and irrigated with hot solutions. The lesion present represented either compromised bowel and mesentery which occupied the hernial sac, or mesenteric thrombosis unrelated to hernia. Because of the poor condition of the patient, the bowel was replaced in the general peritoneal cavity, with the hope of recovery.

January 27, the patient had remained distended and was vomiting.

January 28, a jejunostomy was performed for what clinically was thought to be a paralytic ileus. At operation, all the loops were distended except the primarily involved intestine, which was contracted and red but without evidence of necrosis. There was visible peristalsis. There was no peritonitis. As there was no indication for resection, a typical Witzel jejunostomy was performed. There was some leakage at one point, but this was controlled by suture.

January 31, the patient died, evidently from peritonitis.

At necropsy the proximal 3 feet (91.4 cm.) of jejunum were distended and matted together with fibrinous exudate. The jejunostomy wound was surrounded by purulent exudate. A foot (30.4 cm.) of ileum was deep blue; the wall was thin and friable and tore easily. About 6 inches (15.2 cm.) from the ileocecal valve was another blue area in which the thickness of the intestinal wall was diminished. The mesenteric vessels were investigated and no thrombi found. The appendix was normal. The large intestine was collapsed and the stomach congested. The kidneys showed cloudy swelling with a solitary cyst. The heart was normal.

CASE 4.—A Russian man, aged 48, was admitted, June 13, 1924, to the service of Dr. A. V. Moschcowitz and died, June 19. The diagnosis was strangulated properitoneal hernia, with intestinal obstruction. There also was gangrene of the small intestine. A laparotomy was performed for relief of the strangulation.

The patient had had bilateral hernia for six years and had worn a truss. Three weeks before admission, he noticed that both hernias were irreducible and painful. A physician was called who reduced them. He noticed that the hernias were down and reducible, the left side requiring firm pressure. The patient had felt

well until two days before when he began to vomit and have abdominal cramps. The vomitus was thin, consisting of brown, foul smelling material. No bowel movements or gas passed for two days.

Physical examination showed an old man appearing acutely ill. The heart sounds were weak and of poor quality. There were sonorous râles on both sides of the lungs. The abdomen was moderately distended, soft and tender. There was no visible peristalsis, and no masses were felt. In the inguinal regions, there was a mass on both sides, which was easily reducible.

On operation several loops of small intestine were found collapsed; others were markedly distended. Palpation revealed a tense mass in the left side of the lower part of the abdomen. Further examination of the mass showed it to consist of saclike structure with a narrow constricted neck, inside of which was caught a loop of intestine. After this constriction was incised, the loop was easily withdrawn. A portion of this loop was swollen, black and congested. The serosa was shiny. Peristalsis returned and the vessels pulsated so that the intestine was considered viable. When a finger was inserted into this abdominal sac it was demonstrated that it communicated with the sac in the inguinal canal. The sac from the inguinal canal was inverted and ligated at the neck. The wound was closed in layers.

June 16, there was moderate distention, and the patient was vomiting in small amounts. The bowels moved without enema. The temperature was 100; the pulse, 120-132.

June 18, the wound was clean. Examination of the lungs revealed moist râles throughout the chest.

June 19, the general condition was poor. The temperature was 103; the pulse was very rapid and poor. In spite of stimulation, there was no reaction, and the patient died.

At necropsy the stomach was moderately distended and contained greenish fluid with a fecal odor. In the small intestines, the proximal three or four feet (91.4 or 121.9 cm.) were distended with gas and thin brownish fluid. The surface was dark purple; the mucosa was dark and showed numerous submucous hemorrhages. The remainder of the small intestine was collapsed. A portion of the ileum which had been contained in the left hernial sac was dark purple and almost black, was moderately angulated owing to a fibrinous adhesion and was covered with a thick, patchy exudate. The degree of kinking was not sufficient to cause an actual obstruction. The mucosa was dark purple and there were numerous submucous hemorrhages. The lungs showed evidence of chronic bronchitis and emphysema. The heart showed moderate arteriosclerosis of vessels and valves.

CASE 5.—A man, aged 58, was admitted, June 12, 1923, to the service of Dr. Elsberg and died, June 16. The diagnosis was strangulated, left inguinal hernia, with cellulitis of the abdominal wall, diffuse peritonitis and gangrene of the small intestine. A herniotomy was performed and suture for strangulated, left recurrent inguinal hernia.

A herniotomy had been performed two years before admission in Russia. Two hours before admission, without apparent cause, the patient developed severe pain in the left side of the lower part of the abdomen and a mass appeared in the groin. He vomited after taking castor oil. The bowels moved.

Physical examination showed an old man in pain but not prostrated. The abdomen was distended and tense everywhere, with tenderness in the lower half. In the left inguinal region a tender and irreducible mass was present.

A 3 inch (7.6 cm.) incision was made through the scar in the left inguinal region. The cord was readily freed from the adherent intestine (sigmoid), which

was viable. The free peritoneal cavity was not entered because of the sliding character of the hernia. This was followed by a laparotomy for 2 inches (5 cm.) above the internal ring, but the peritoneal cavity could not be entered. A layer closure of the incision was made. The material between the folds of the intestine was at first thought to be purulent, but not enough was obtained for verification. Owing to the extreme rigidity of the abdominal wall at the time of examination, there was a suspicion of the presence of peritonitis; an abdominal puncture was made in the left, lower quadrant of the abdomen.

June 15, there was tenderness over the entire abdomen; the wall was edematous. There was subcutaneous emphysema, and the wound was exuding brownish red serum of foul odor. The wound was opened and the pus evacuated. Welsh's bacillus and hemolytic streptococcus were present.

Multiple incisions were made and drainage was done. There was gas gangrene of the abdominal wall, and the entire abdominal wall contained foul, purulent material. The fascia and muscle were necrotic.

At midnight the general condition was worse; the skin was cold and clammy and the pulse imperceptible.

June 16, pulmonary edema and cyanosis were followed by death.

At necropsy the abdominal wall showed multiple incisions and was edematous and discolored. On palpation crepitation was felt. None of the incisions communicated with the peritoneal cavity. The abdominal cavity showed greenish red omentum. Loops of small intestine were lying in the midabdomen, one somewhat distended; while in the left, lower quadrant the small intestines were collapsed and matted together by a fibrinopurulent exudate. In this mass one loop showed a perforation which discharged intestinal contents. Similar fecal fluid was collected in the pelvis. There was no free fluid in the lumbar gutter. There was fibropurulent exudate over the major portion of the small intestine, the cecum and the ascending and transverse colon. The pylorus and duodenum were negative. The jejunum was dilated, with its peritoneal surface showing fibropurulent exudate, while the mucosa showed some pin point hemorrhagic areas and, in parts, a greenish purple appearance, probably gangrenous. Near the terminal portion of the ileum about 11 feet (335 cm.) from the ileocecal junction the fibropurulent exudate was thickened and surrounded a perforation about 2 mm. in diameter. The mucosa in this area was gangrenous.

The diagnosis was acute cellulitis of the abdominal wall. *Bacillus aërogenes* was present. There was acute, diffuse, purulent peritonitis with perforation of the ileum, an incomplete intestinal obstruction due to adhesions, and gangrene of the small intestine.

CASE 6.—A man, aged 50, was admitted, Aug. 25, 1923, to the service of Dr. A. A. Berg and died, August 25. The diagnosis was strangulated, right inguinal hernia, with intestinal obstruction.

The patient had had a right sided hernia for the last fifteen years. Twelve hours before admission, he developed pain in the right groin, abdominal distention and general weakness, but he did not vomit. Although the mass was always large and irreducible, it had increased in size.

Physical examination showed a middle aged man, acutely ill. The chest was barrel-shaped, and there were hyperresonant, sonorous and sibilant râles all over the chest. The abdomen, which was greatly distended, was tender and slightly rigid in the lower half. There was no visible peristalsis. The scrotum was about the size of a football, tense and covered with enlarged and engorged veins. It was dull on percussion. In the right inguinal canal was a mass continuous with that in the scrotum.

On operation a greatly distended scrotum was revealed containing a considerable amount of slightly turbid fluid and ten coils of small intestine, half of which

were collapsed, the other half distended, a large portion of omentum, transverse and ascending colon. There was no constriction of the ring.

Resection was done of a large mass of omentum and reduction of the small intestine. The large intestine was left in the sac, which was closed, leaving 2 inches (5 cm.) of colon for future colostomy. The wound was closed in layers.

The patient suddenly went into collapse after vomiting, he became cyanotic and the pulse irregular. Stimulation was given with no effect; he died.

On necropsy the lungs showed congestion and edema but no consolidation. The heart was enlarged; the valves and coronary arteries showed evidence of arteriosclerotic changes. In the region of the right iliac fossa and the scrotum there was a large, smooth, bulging mass having the appearance of an inguinal hernia. When the abdominal cavity was opened, the small intestine was found to be greatly dilated and its walls thin, tense and congested. The mass in the lower quadrant was found to be a hernial sac and contained the ascending colon and 0.5 of the transverse colon. This part of the intestine was hugely distended and the walls were deep purple. There had been obstruction of the ascending colon at a point midway between the cecum and the hepatic flexure due to compression and strangulation at the point of entrance into the hernial sac. The diagnosis was acute intestinal obstruction due to strangulated, right inguinal hernia.

Case 7.—A man, aged 60, was admitted, Oct. 26, 1923, to the service of Dr. A. V. Moschcowitz and died, October 27. The diagnosis was strangulated, recurrent, left inguinal hernia, with coronary sclerosis. Hernioplasty was done.

In 1914-1915, the patient had been operated on for bilateral inguinal hernia. Both recurred one month after operation. Three days before admission, the patient was suddenly taken with severe pain in the lower abdomen and vomited. He had been constipated and passed no gas since the onset. Medication and enemas had no effect.

Physical examination showed the patient to be well developed and acutely ill. The chest showed evidence of emphysema. The heart was somewhat enlarged. The sounds were distant, the aortic second being accentuated. The abdomen was distended, tender and rigid, particularly in the lower half. Several large masses in the lower abdomen, one about 8 by 3 inches (20.3 by 7.6 cm.), passed over the right side of the pubic ramus between the symphysis and the anterior superior spine and descended downward and mesially into the scrotum. Another smaller mass was situated on the opposite side. In addition, there were two rounded masses each about 4 inches (10.1 cm.) in diameter in the left hypogastric region. The skin over these masses was discolored and there was evidence of scar.

An inguinal incision was made. The sac was lobulated and contained small and large intestine adherent to the sac. This was liberated. The large intestine, which was strangulated in two places, was freed. The sac was excised and closed. A layer suture was made.

October 26, the patient was in fair condition after the operation. Shortly after, he developed symptoms of cardiac failure and became cyanotic; the pulse was rapid and weak. Moist râles were noted in the chest. In spite of stimulation, he ceased breathing four hours after the operation.

At necropsy the wound was clean and firm. The abdomen was negative except that the small and large intestines were moderately distended. The musculature of the right and left ventricles of the heart was soft, thin and flabby. The mitral and aortic valves showed patches of arteriosclerosis. The anterior descending coronary artery was arteriosclerotic and calcified and the lumen almost completely occluded at a distance of 2 cm. from the beginning of the vessel. The other branches of the coronary arteries showed a moderate degree of arteriosclerosis. The aortic elasticity was gone. Many arteriosclerotic patches and ulcers were present. The diagnosis was arteriosclerosis of the coronary vessels.

CASE 8.—L. H., a man, aged 85, whose mother had been born in Germany, was admitted, April 13, 1922, to the service of Dr. A. V. Moschcowitz and died, April 14. The diagnosis was strangulated, left direct inguinal hernia, with the postoperative complications of myocarditis and pulmonary edema. An Andrew-Ferguson hernioplasty was done. The patient had had a hernia on the left side for twenty years. For the last week this had been irreducible. The patient had vomited on and off for about seven days and for the last two days had had general abdominal pain. The bowels had not moved for three days.

Physical examination showed an old, emaciated man, evidently acutely ill. During the course of the examination, the patient expectorated a rusty fluid sputum. The lungs showed evidence of congestion. In the right groin there was a bulging, tympanitic mass which was irreducible.

April 13, a 4 inch (10.1 cm.) inguinal incision was made under procain anesthesia. The sac was found to be of a direct variety and contained a strangulated loop of small intestine, which was dark purple with omentum adherent in one area. Part of the omentum also was strangulated. The sac was carefully exposed and the adherent omentum was divided between ligatures, the distal piece being permitted to remain on the intestine. The constricting ring was cut and the intestine, which appeared viable, was replaced. An Andrews-Bassini hernioplasty was done. During the operation, the patient coughed and vomited considerably and was slightly cyanotic.

April 14, the general condition was poor and the patient moderately cyanotic. April 15, he died.

On exploring the abdomen at necropsy, the loop of ileum was found to be deeply congested and hemorrhagic, with a small piece of adherent omentum. The proximal end of the omentum had been ligated with catgut. The heart showed evidence of myocarditis. The lungs showed scattered areas of bronchopneumonia and there was a general arteriosclerosis.

CASE 9.—I. W., a man, aged 77, whose mother was born in Russia, was admitted, Jan. 4, 1924, to the service of Dr. A. V. Moschcowitz and died, January 6. The diagnosis was strangulated, left indirect inguinal hernia, with myocarditis, emphysema and gangrene of the intestine. An Andrews-Bassini hernioplasty was done.

The patient had had an inguinal hernia for more than thirty years, and had suffered from repeated attacks of pain in the inguinal region. Two years before admission, this attack seemed to last for about four days. Four days before admission, the patient began to vomit and this had persisted. There had been no bowel movement for four days, although enemas had been partially effective. Physical examination showed an old man of about 70, acutely ill, cyanotic and vomiting dark brown material. The temperature, pulse and respiration were normal. The lungs showed evidence of emphysema and the heart was definitely enlarged. There was a reducible hernia on the right side, but on the left side this mass, which extended into the scrotum and was about the size of a grapefruit, was irreducible.

January 4, under local anesthesia, a 4 inch (10.1 cm.) inguinal incision was made. When the hernial sac was opened, about 4 ounces (118.4 c.c.) of bloody fluid and a loop of small intestine with hemorrhages were visible. After the constriction was relieved, the contents were thought viable and were reduced and an Andrews-Ferguson hernioplasty was performed.

January 5, the condition seemed good. The patient had had involuntary bowel movements. January 6, the patient was found dead in bed.

When the abdominal wall was incised at necropsy, the peritoneal cavity contained a liter of hemorrhagic fluid. The appendix appeared normal. The small

intestine, from a point 6 cm. distal to the duodenojejunal junction to a point 8 cm. proximal to the ileocecal junction, was bluish black, distended and contained a large amount of free fluid. The veins in the serosa of the small intestine stood out prominently but were not thrombosed. When the superior mesenteric artery was dissected out, there was found a small embolus, 3.5 cm. from its origin, producing complete occlusion. The smaller branches did not show other emboli or areas of thrombosis. The small intestine, on section, showed necrosis throughout the area described. From a point about 10 cm. from the ileocecal junction in the gangrenous small intestine was an area about 4 cm. in length, with marked hemorrhage, between the leaves of the mesentery; this had a formation of smooth, firm, black tumor that on section apparently was composed of clotted blood and did not involve the mucosa of the intestine. This presumably was a portion of intestine that was caught in the hernial sac. The large intestine showed no gross abnormality. The remainder of the necropsy disclosed a chronic, interstitial myocarditis, aneurysm of the heart and thrombosis of the left ventricle.

CASE 10.—A. G., a man, aged 67, whose mother was born in Turkey, was admitted, June 17, 1924, to the service of Dr. A. V. Moschcowitz and died the same day. The diagnosis was strangulated, right inguinal hernia, with no complications. An Andrews-Bassini hernioplasty was done, and there was postoperative intestinal obstruction.

For the last ten years, the patient had had an inguinal hernia which had always been reducible and for which he had never worn a truss. Nine hours before admission the mass suddenly became irreducible and the patient developed pain in the groin. He vomited several times. The bowels moved two hours before admission.

Physical examination showed a man of about 65, acutely ill. The temperature was 99.2; pulse, 92, and respirations, 24. The abdomen was soft and lax and not tender. In the inguinal scrotal region was a mass measuring 7 by 5 by 3 inches (17.7 by 12.7 by 7.6 cm.), which was tense and irreducible.

June 17, a 4 inch (10.1 cm.) inguinal incision was made under procain anesthesia. The sac contained some amber fluid and a loop of ileum, 10 inches (25.4 cm.) in length, which was normal in color. Examination of the ileocecal region showed that the ileum was bluish black, the cecum markedly dilated and the appendix covered with fibrin but not acutely inflamed. The mass was constricted at the internal ring. When the constriction was relieved, the application of hot saline solution to the ileum caused the normal color to return slowly. Peristalsis was present and pulsations were felt in the vessels of the mesentery. The intestine was thought viable and was reduced. An Andrews-Bassini hernioplasty was then done.

Twelve hours after the operation, the patient attempted to get out of bed and went into profound shock, dying a few hours later.

When the peritoneal cavity was opened at necropsy, there was about 1½ liters of brownish, thin fluid. All the intestines from the transverse colon to the duodenojejunal junction were considerably distended. They were covered by a thin fibrinopurulent exudate, particularly about the appendix. In the ileum, about 1 foot (30.4 cm.) from the ileocecal valve and extending for about 2 feet (60.9 cm.), the intestine was blackish red, friable, and covered by a thin, greenish, fibrinous exudate in many places. When the large intestine and part of the small were opened, a large amount of thick reddish fluid was obtained. The mucosa at the site of the necrotic intestine was deeply injected and black. The mesenteric vessels contained no thrombi, except at the site of the strangulated intestine, where the minute venous capillaries contained a few postmortem thrombi. The remainder of the necropsy disclosed a general arteriosclerosis and chronic bronchitis.

From the clinical records of fourteen cases and the necropsy reports of eight, it was evident that the immediate cause of death was either intestinal obstruction, peritonitis or a combination of both. This indicates quite clearly and definitely that although experience would lead one to believe that the tissues were viable from certain macroscopic findings, death was present microscopically and that following operation there was a progressive destruction of the bowel wall, resulting in gangrene. The patients who succumbed were usually more than 50, a period of life in which sclerosis of the blood vessels manifests itself and an age in which thrombosis with its subsequent pathologic changes is apt to occur. The more conservative treatment in these cases in which the viability of the strangulated intestine was questionable would have been the more radical, and the mortality of 30 per cent. might have been lowered. In doubtful cases, most surgeons are loath to resect and probably with great justification. They have inherited the theory that it is better to rely on nature and hope for spontaneous recovery of the bowel than to perform an enterectomy with its high mortality. But they have been blind to one essential fact. The mortality in intestinal resection was certainly high; however, it was high not because of the operation but because those cases in which it was performed had already reached the stage of frank intestinal gangrene with complete obstruction. The majority of these patients had already received a lethal dose of intestinal poisoning, and most of them would have died from the effects of intestinal obstruction, no matter what procedure was instituted.

When viability of the intestine is questionable, resection need not be performed as a matter of routine because the involved bowel, adequately protected, may be left exposed in the wound for from six to eight hours before deciding its fate. This procedure is quite rational; it certainly is practical and might solve many doubtful cases. On several occasions, the loop of questionable intestine, although replaced in the peritoneal cavity, was identified by a piece of chromic catgut passed through the mesentery, the free end of the suture being permitted to protrude through the operative incision. With this guide, the damaged intestine can easily be drawn into the wound and a rapid resection performed, should the emergency arise.

When the bowel is gangrenous in patches, as frequently occurs in a Richter hernia, the involved portion may be infolded and carefully covered with a Lembert's suture. However, when the intestine is completely compromised, resection is the operation of choice, provided the condition of the patient will permit it. A side-to-side anastomosis either by suture or by Murphy button is the preferable method of enterectomy. While an enterostomy can be performed in less time, it is ultimately undesirable and is attended usually by a fatal issue. This occurred in the four cases in which it was tried. It should really be

done as a last resort and only in those patients who will not tolerate a more extensive procedure. In desperately ill patients with very large inguinoscrotal hernias, simple division of the constricting element without opening the peritoneal sac should be employed whenever possible. This was done in five cases. It simply relieves the intestinal obstruction. As a rule, any attempt to reduce these contents is either impossible or so shocking that death rapidly follows.

From a study of the causes of death, it becomes quite apparent that intestinal obstruction is responsible for a great number, and it is an open question whether in some of these cases in which there has been definite obstruction for more than twelve hours, and in which at the time of operation a portion of the bowel proximal to the obstruction is definitely dilated, a jejunostomy might not be advisable. This simple procedure

TABLE 8.—*Operations*

	Inguinal	Femoral	Umbilical	Ventral
Hernioplasty	124	82	24	12
Incision	4	1	0	0
Laparotomy	3	2	0	0
Resection, intestine	4	17	1	0
Resection, omentum	11	9	7	4
Appendectomy	4	..	..	..
Enterostomy	1	2	1	0

Summary

	Total Number	Resections, per Cent.
Hernioplasty	230	..
Incision	5	..
Laparotomy	5	..
Resection, intestine	22	11
Resection, omentum	30	36
Appendectomy	4	..
Enterostomy	4	..

certainly gives drainage to the lethal poisons of the higher bowel and the general toxemia of the patient is definitely lessened and the recuperative powers markedly increased.

Of 187 cases of strangulated bowel, resection was deemed necessary in twenty-two cases, only 11 per cent., with a mortality of 40 per cent. This is a high mortality, but it must be remembered that these cases were frankly gangrenous and exceptionally poor operative risks because of a prolonged period of intestinal obstruction. In eighty-two cases in which the omentum was strangulated, thirty, or 36 per cent., were resected with only three deaths. In Table 8, the various operative procedures are listed.

After the herniotomy has been performed a hernioplasty may be done provided the patient's condition permits. In the inguinal variety the plastic operation used was either an Andrews-Bassini or an Andrews-Ferguson; in the femoral hernias, a Moschcowitz or Lotheisen was employed, and in the ventral and umbilical hernias the typical Mayo operation was performed.

The postoperative complications were surprisingly small. There were fifteen cases of respiratory infections, seven wound infections, twelve hematomas, one femoral and one pulmonary embolism.

The causes of death are tabulated in Table 9. Of the thirty-six deaths, twenty-three were accounted for by a combination of shock and intestinal obstruction; four by peritonitis; two by cardiac failure, and

TABLE 9.—*Causes of Deaths in Strangulated Hernia*

Inguinal		
Shock following resection (cardiac failure)	2	
Intestinal obstruction (also bronchopneumonia)	6	
Tetany	1	
Coronary sclerosis	1	
Acidosis	1	
Infection of scrotum	1	
Diffuse peritonitis	2	
Nonoperated intestinal obstruction	1	
	—	15
Femoral		
Shock following resection	5	
Intestinal obstruction	5	
Bronchopneumonia	1	
Peritonitis	2	
Empyema of gallbladder	1	
	—	14
Umbilical		
Shock	1	
Intestinal obstruction	4	
Cardiac failure	1	
Diabetic coma	1	
	—	7
Ventral hernia		0
		36

TABLE 10.—*Mortality in Strangulated Hernias, 1913-1923*

Hernia	Number	Operated	Not Operable	Cured	Died	Per Cent.
Inguinal	142	133	9	118	15	10.4
Femoral	96	95	1	81	14	14.6
Umbilical	26	26	0	19	7	26.5
Ventral	12	12	0	12	0	0
Epigastric	1	1	0	1	0	0
Properitoneal	1	1	0	1	0	0
Total	278	268	10	232	36	12

one by bronchopneumonia. In other words, of those who succumbed, 67 per cent. died probably from the effects of their intestinal obstruction. In Table 10 the mortality figures of the various groups are given. The total mortality for this series of 278 cases was about 12 per cent. In the inguinal hernias, it was 10 per cent.; in the femoral 14 per cent., and in the umbilical 26 per cent.

Early operation and local anesthesia are great factors in the diminution of operative mortality. Whether jejunostomy and more frequent resection might reduce the mortality in those cases that have been strangulated beyond twelve hours remains to be seen.

CAN PLEURAL EFFUSIONS FOLLOWING THORACOTOMIES BE PREVENTED BY ARTIFICIAL PNEUMOTHORAX?*

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Some remarkable results were reported by an Italian surgeon, Morelli,[1] in the treatment of war wounds of the lung and pleura by means of artificial pneumothorax. He asserts that he had a mortality of only 5 per cent. in penetrating gunshot injuries of the thorax, as compared with the 30 per cent. mortality of the English and American armies. It was with a view of determining whether his procedure could be applied with advantage after operations within the thorax that this study was undertaken.

HISTORY

Artificial pneumothorax is by no means a new procedure. As early as 1822, James Carson of Liverpool suggested its use and experimented with its effect on the circulation. In 1882 Forlanini introduced it in the treatment of pulmonary tuberculosis. He later proposed its use for lung abscess, bronchiectasis, and finally for tuberculous pleural effusions. Experimental studies on dogs of the effect of pneumothorax on pleural infection were carried on as early as 1906 by Noetzel[2] of Frankfort. In 1910, Morelli, a former student of Forlanini, published his thesis on spontaneous perforation of the lung and enunciated the principle, which he later applied in the treatment of war wounds of the lung and pleura. Murphy[3] was foremost among those in this country to use pneumothorax therapeutically.

THE PROBLEM

The purpose of this work was to determine whether pleural effusions following thoracotomy, which is at present the most difficult complication of thoracic surgery to overcome, could be controlled by postoperative artificial pneumothorax.

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*The experiments were conducted in Stanford University School of Medicine surgical laboratory.

1. Morelli, E.: Wounds of the Lung and Pleura, translated by Davis and Irving, 1920.

2. Noetzel, W.: Ueber die Infection und die Bacterien resorption der Pleura hohle, Experimental Untersuching, Arch. f. klin. Chir. **80**:679, 1906.

3. Murphy, J. B.: Surgery of the Lung, 1898.

Morelli suggested a theory for the production of such exudates which has been quite widely accepted. He supposed that the pleural effusion results from the aspirating effect of the negative intrapleural pressure on the edematous pleural surfaces and underlying tissues. As the thoracic wall expands on inspiration and the diaphragm descends, because of the inherent elasticity of the lung, the negative pressure in the potential pleural cavity increases. On expiration the pressure rises. In the human being, this fluctuation of pressure has been determined by MacLeod [4] to be from —5 mm. of mercury on expiration to —10 mm. of mercury on inspiration. Aron's [5] figures are slightly lower, from —3 to —4.5 approximately. Morelli and others believe that the transudate oozes out of the tissue during the period of maximum negative pressure. Graham [6] through experiments on the isolated lung, in a glass case, found that during the phase of maximum negative pressure a saturation of the tissues with fluid occurred, and that this fluid is expressed into the pleural sac during expiration in the phase of least negative pressure.

PROCEDURE

At first we planned to operate on two groups of dogs, under similar conditions, denuding an equal area of visceral pleura in each and then closing the pleural cavity hermetically. In the one series, we planned to aspirate all the air from the pleural cavity, thereby reestablishing the normal intrapleural pressure. In the other group, we planned to close the pleural cavity and subsequently immediately to introduce enough air to establish a positive intrapleural pressure. The amount of pleural effusion resulting from these two procedures was then to be determined by means of roentgen-ray and physical examinations, aspiration and necropsy.

RESULT OF POSITIVE INTRAPLEURAL PRESSURE

The first dog (Dog 1), in which a positive intrapleural pressure of 16 cm. of water was induced, died about an hour and thirty minutes after operation. Following the introduction of air his breathing was quite deep and labored. As necropsy revealed no other cause of death, it was evident that asphyxia and its resulting strain had been responsible for this death.

Dog 10, in which following operation enough air was introduced to establish a pressure oscillating from —4 to +4 cm. of water, also died

4. MacLeod, J. J. R.: Physiology and Biochemistry in Modern Medicine, Ed. 2, 1918, p. 305.

5. Aron, quoted by Emerson, C. P.: Pneumothorax, Bull. Johns Hopkins Hosp. **11**:1-450, 1903.

6. Graham, E. A.: Recent Phases of Thoracic Surgery, J. A. M. A. **80**:1825 (June 23) 1923.

one and one-half hours after operation. Here, too, there was labored breathing and necropsy again showed no other cause of death.

Others also have found that dogs die following the induction of artificial pneumothorax.

DO RESULTS FROM DOG EXPERIMENTATION APPLY TO THE HUMAN BEING?

Duval [7] states that death following artificial pneumothorax is due to the fact that in a dog a communication exists between the two pleural cavities, that there is an opening in the mediastinum; hence, he maintains that air injected on one side immediately passes through to the other pleural cavity, and under such conditions cannot be tolerated.

We have never been able to find such an opening. Graham [6] states that he has examined twenty-five dogs and failed to discover any communication between the two pleural cavities. Dyestuffs have been injected on one side and have not appeared in the opposite pleural cavity. The mediastinum in dogs, as well as in human beings, forms an effective barrier to massive exudates, which commonly are but unilateral. Therefore, the objection to the dog as an experimental animal for this work, from the standpoint of the existence of an opening in the mediastinum, cannot be looked on as a valid one.

It must be granted that the dog has a flexible, yielding mediastinum. We have injected air on one side of a recently killed dog and have found that the pressure in the opposite pleural cavity was only slightly below that on the side in which the air was injected. When the pressure on the injected side was 10 cm. of water, that in the opposite pleural cavity was 9.5 cm.

Graham [8] has shown that a similar thing occurs when a warm human cadaver is used; namely, that a pressure induced on one side produces a pressure of almost equal degree within the opposite side. Simon [9] and Betchov,[10] in their experimental studies on human beings and animals on the effect of pneumothorax on pressure conditions in the opposite side, also have found that the normal mediastinum is not of sufficient strength to permit of any substantial difference in pressure on the two sides. Therefore, when the mediastinum has not been thickened or stabilized by a preceding inflammation, the thoracic cavities, as far as pressure relationships are concerned, must be considered as one large

7. Duval, P.: Les donneés actuelle de la chirurgie intrathoracic unilaterale en pleura libre, Presse méd. **30**:409 (May 13) 1922.

8. Graham, E. A., and Bell, R. D.: Open Pneumothorax: Its Relation to the Treatment of Empyema, Am. J. M. Sc. **156**:839 (Dec.) 1918.

9. Simon, S.: Am. Rev. Tuberc. **5**:620 (Oct.) 1921.

10. Betchov, N.: Schweiz med. Wchnschr. **51**:43 (Oct.) 1921.

cavity. As this is true for the human being, as well as for the dog, the dog can be used for experimental purposes.

If conditions are such that the thorax is virtually one large cavity, how is ventilation of the lung effected when a positive intrapleural pressure is induced? How can one explain Morelli's experience with the use of positive intrapleural pressure, which he employed in so many cases in the treatment of war wounds of the lung and pleura? In one of his cases, he injected enough air to produce a positive pressure of +18 cm. of water. Surely one cannot presuppose that a previous fixation of the mediastinum had occurred in all of his cases in which he employed this method, especially as his cases were those of healthy young soldiers.

We found that a dog could live for a short time with a positive intrapleural pressure of a considerable degree. Under these circumstances, there is apparently a compensatory increase of inspiratory effort, as shown by the slow, deep, labored breathing. Eventually, the animal succumbs owing to exhaustion.

Yates believes that it is possible to induce a pneumothorax with a substantial positive pressure which will be confined to one side, as long as the circulation remains competent. When the blood pressure falls, he maintains that the pressure on the two sides becomes equal.

Clinical observations in the use of positive pressure and theory have not been entirely reconciled. It is difficult for us to understand how a human being can live with such a degree of pleural pressure when dogs cannot long exist with a positive intrapleural pressure.

PLEURAL REFLEX

Numerous instances have been reported of severe dyspnea and even sudden death occurring during paracentesis when the pleura was penetrated. These have been explained on the basis of the existence of a pleural reflex. Duval has suggested the theory that dyspnea, occurring during the thoracotomy operations, is partially due to the irritation of the pleura by the air entering and being expelled from the opened pleural cavity during the respiratory excursions of the thoracic wall. He maintains that this dyspnea can be controlled by quickly fixing the thoracic wall and compressing all the air out of the partially collapsed lung of that side. In our experiment, in which the pleura was extensively traumatized by tearing, cauterizing with heat and curetting, no direct ill effects or shock from such injury were seen.

SUBCUTANEOUS EMPHYSEMA

In those dogs in which air was injected after the chest wall was closed, a subcutaneous emphysema in the vicinity of the wound occurred almost invariably. This was exceedingly difficult to prevent,

TABLE 1.—*Dogs with Pneumothorax*

Dog	Procedure Within Thorax	Degree of Pneumothorax, as Shown by Intrapleural Pressure	Amount of Pleural Effusion, C.c.	Results
1	Visceral pleura denuded over 28 sq. cm.	Positive pressure +14	0	Dog died of asphyxia and exhaustion 2 to 3 hours after operation; breathing labored after pneumothorax; necropsy showed no blood or fluid; both lungs collapsed
4	Visceral pleura denuded over 2 by 1 in. (5 by 2.5 cm.); two ribs sawed longitudinally, exposing oozing marrow on internal surface	+4 to −4	0	Postoperative condition poor; respiratory distress; considerable subcutaneous emphysema; no fluid at necropsy
5	Cauterization by heat with subsequent curetting of cauterized 40 sq. cm. surface	+2 to −2	+	Some respiratory distress; extensive subcutaneous emphysema; 30 c.c. of fluid aspirated on third day; high fever, 105.6, developed; dog died on fifth day; large amount of thin serosanguineous fluid in left pleural cavity; left lung partially collapsed; few adhesions between visceral pleura and traumatized area; right pleural cavity contained small amount of similar fluid
8	Same as in Dog 5	+3 to −3	23 c.c.	Postoperative condition good; 23 c.c. serosanguineous fluid aspirated on second day; uneventful recovery; dog killed about 3 weeks after operation; no fluid; lungs appeared normal, except for adhesions between visceral pleura and traumatized areas
9	Same as in Dog 5	+6 to −6	130 c.c. second day	Postoperative condition fair; after aspiration of fluid on second day no further fluid developed; dog had an attack of pneumonia, but recovered completely, roentgen-ray examination on third day showed a large left sided pneumothorax and a small right sided pneumothorax as well
10	Same as in Dog 5	+4 to −4	0	Breathing labored after injection of air; dog died one and one-half hours after operation; necropsy showed no hemorrhage or fluid; death due to shock of pneumothorax
11	Same as in Dog 5	−1 to −5	0	Postoperative condition fair; moderate subcutaneous emphysema; no fluid ever developed; roentgen ray revealed pleural adhesions at left base and apex; good recovery
17	Extensive area of visceral pleura cauterized without curetting	0 to −4	Large amounts, 35 c.c. 1st day; 300 c.c. 3d day; 250 c.c. 6th day; 260 c.c. 8th day	Postoperative condition fair; large amounts of serosanguineous fluid continued to form; even after eighth day fluid formed, but escaped through a small sinus which formed; temperature varied from 102 to 106; dog killed after 1 month; necropsy showed a moderate sized cavity lined by thickened pleura, filled with serous exudate
18	Same as in Dog 17	0 to −4	40 c.c. 1st day; none 3d day; large amounts of fluid after this	On the third day no fluid was obtained on aspiration; however, 2 days later large amounts of thin, purulent secretion began to form and continued to drain from a small sinus through the wound; necropsy 1 month later, after sinus had closed, showed condition same as in Dog 17

even by extra buried sutures approximating the subcutaneous tissues. However, it seemed to have no ill effect either on the healing of the wound or otherwise.

METHOD OF PRODUCING PLEURAL EFFUSION

Pleural effusian does not result invariably when the pleura is damaged. Indeed, one of the difficulties encountered in our work was to find some method of constantly producing fluid. Merely denuding the chest wall of the pleura was unsuccessful. Even when, in addition to stripping away the pleura over a considerable area, a rib was sawed longitudinally so that raw bone marrow was exposed to the aspirating effect of the negative pressure, no fluid resulted. Cauterizing by heat and then immediately curetting an extensive area of pleura in some cases produced fluid, but in others no fluid, or only small amounts of it. However, when cauterization by heat alone was resorted to, as in the last five cases, considerable amounts of fluid resulted.

In the last four experiments (Experiments 15 to 18 inclusive) the visceral pleura was merely cauterized and the incision was closed. In Experiments 15 and 16 all the air was aspirated. In Experiments 17 and 18 the intrapleural negative pressure was reduced by allowing the air to remain. This constitutes as marked a degree of pneumothorax as we had found to be tolerated with safety. All four dogs developed large pleural effusions, there being as much, or possibly more, fluid formed when the air was left in as when it was aspirated. The exact amounts could not be determined, as the first two dogs died and in the last two some of the fluid was lost by leaking through the wound to the surface.

In Dogs 12 and 13, the visceral pleura was cauterized by heat and subsequently curetted; then after the thorax was closed, all the air was aspirated. Only small amounts of fluid formed. This result was probably due to the fact that in these cases adhesions formed early between the visceral and the parietal pleura. Other dogs, earlier in the series, in which no fluid was obtained, on necropsy showed well marked adhesions between the visceral and the parietal pleura.

It was observed almost invariably throughout the entire series that air left in the pleural cavity caused a considerable postoperative respiratory distress. Those dogs in which the air was aspirated were apparently far more comfortable and breathed less laboriously.

DETAILS OF THE EXPERIMENTS

Morphin was given about two hours before operation, from 1½ to 2 grains (0.09 to 0.13 gm.), depending on the size of the dog. The dogs were then anesthetized by means of the ether cone. When sufficiently narcotized to permit, a catheter was inserted into the trachea

as far as the bifurcation, approximately, and the anesthesia and inflation of the lung were maintained by the Auerbach-Meltzer method. An intratracheal pressure of about 14 cm. of water was found adequate to keep the lung inflated after the chest wall was opened.

The thoracic wall was opened through the eighth intercostal space by an incision extending from the angle of the ribs posteriorly and

TABLE 2.—*Dogs Without Pneumothorax* *

Dog	Procedure Within Thorax	Amount of Pleural Effusion	Results
2	Visceral pleura denuded over area, 28 sq. cm.	0	Excellent postoperative condition; uneventful recovery
6	Cauterization with heat and subsequent curetting of 40 sq. cm. of visceral pleura	40 c.c. 2d day	No fluid on first day; dog died of bronchopneumonia on second day, as shown by necropsy; some adhesions between lung and upper part of traumatized area
7	Same as in Dog 6	150 c.c. 2d day 95 c.c. 3d day	Postoperative condition good; uneventful recovery with no further formation of fluid after third day, according to roentgen-ray examination; smears and cultures of fluid showed gram-positive cocci in short chains and bunches
12	Same as in Dog 6	35 c.c. 1st day	Postoperative condition good; after aspiration of fluid on first day, no more formed and an uneventful recovery occurred
13	Same as in Dog 6	22 c.c. 2d day	Postoperative condition good; no fluid after second day; dog developed a pneumonia on the fourth day but recovered
14	Cauterization without curetting of extensive area of visceral pleura	No fluid 1st day	Dog died while being moved for roentgen-ray examination on second day; left pleura contained 175 c.c. of blood, partially clotted; hemorrhage due to slipping of ligature on intercostal artery
15	Same as in Dog 14	No fluid 2d day	Dog died on fourth day; necropsy showed left pleural cavity full of serosanguineous fluid, with considerable fibrin adhering to all surfaces; left lung collapsed by fluid; right pleural cavity also contained some serosanguineous fluid
16	Same as in Dog 14	5 c.c. fluid 1st day; 65 c.c. fluid 3d day; 85 c.c. fluid 5th day; considerable amount of fluid found at necropsy on sixth day	Dog developed a fever which rose to 105; appeared to be dying, so was killed on sixth day; necropsy showed large amount of serosanguineous exudate, with large fibrinous masses in the left pleural cavity, lung collapsed by fluid with the exception of its upper part, which was adherent to the chest wall, no areas of consolidation, no air in pleura, and right lung and pleura normal

* All the air was aspirated from the pleural cavity after the thoracic wall was closed, thereby reestablishing normal negative intrapleural pressure.

about 2 cm. anteriorly. The ribs were then spread by means of a self-retaining rib spreader. After the various procedures described in the individual reports, the incision was again closed by means of figure of eight silkworm sutures, which approximated the ribs and soft parts. Care was exercised to include sufficient tissue to close the pleural cavity as hermetically as possible. After closure, the intratracheal catheter

was withdrawn. As the lungs were never fully inflated, during the foregoing procedure, air always remained in the pleural cavity.

The dogs were examined fluoroscopically and roentgenograms were taken twenty-four or forty-eight hours after the operation to determine the amount of fluid formed. In addition to this, as physical examination of a dog's chest is not very satisfactory, the chests were aspirated in many cases. Temperatures were taken daily. From our experience in taking preoperative temperatures we concluded that anything less than 101 degrees F. was within the limit of normal for a dog.

As it is impossible to estimate the amount of air left in the pleural cavity, the degree of pneumothorax must be judged by the reduction of the intrapleural negative pressure. Normally this oscillates between —2 and —8 in the dog. An improvised Robinson apparatus was used for injecting air or measuring the intrapleural pressure.

PNEUMOTHORAX AND PLEURAL INFECTION

Noetzel [8] in 1906 did an extensive series of experiments on dogs to determine the effect of pneumothorax on pleural infection.

He had previously demonstrated that the natural resistance of the pleura, under normal conditions, was considerably greater than that of muscle and connective tissue. Injections of cultures of staphylococci, which produced abscesses in muscle and connective tissue, were readily cared for and left no trace in the pleura. Clinically, the favorable course of uncomplicated gunshot and puncture wounds of the pleura was pointed to as evidence of the resistance of this structure.

However, he remarks that the frequency with which infection is encountered, following operations in the pleural cavity, shows that this resistance is substantially impaired by these operative procedures. He believed that the responsible factor was the resulting pneumothorax. This reduced the resistance in two ways: (1) The blood and lymph circulation was disturbed; (2) a dead space was formed, in which an exudate arose and in which detritus collected.

To prove his contention experimentally, he injected cultures of staphylococci and streptococci into the pleural cavities of two series of dogs. In the first series, he avoided a pneumothorax; in the second series he created a pneumothorax by a variety of means. The subsequent course of events was determined by killing the dogs at certain intervals afterward and examining them, as he felt that clinical signs and symptoms were not reliable enough.

His results were quite striking. The dogs without pneumothorax in the large majority of cases were found to have a healthy sterile pleura after five or six days. When killed earlier, a few adhesions or a small amount of fluid was formed. Culture of this gave sparse colonies.

The dogs in which a pneumothorax was associated with the injection of the same cultures after a short time developed severe fibrinopurulent pleurisy. The injected organisms could be recovered in pure culture. The process, furthermore, tended to spread and involve the opposite pleura and the pericardium as well.

Noetzel's results show convincingly that infection flourishes much more in the presence of a pneumothorax.

Some further experiments of his with cultures of *Bacillus pyocyaneus* demonstrated that organisms are absorbed rapidly from the pleural surfaces. However, he believed that the resistance of the pleura was due to a dissolution of the organisms in the pleural exudate and not to their absorption and destruction in the blood stream.

CONCLUSIONS

1. If the artificial pneumothorax is under sufficient pressure to equal the dog's greatest inspiratory effort, the aspirating effect in producing pleural effusions will, of course, be prevented. Such a pressure is plainly incompatible with life, as it would prevent air from entering the lungs. If even much lesser pressures were used the dogs would die from interference with ventilation. From our experiments we conclude that not enough pressure can be used in artificial pneumothorax either to prevent or to lessen the formation of pleural effusion, which so frequently jeopardizes our results following thoracotomy.

2. The old procedure of producing adhesions between the visceral and parietal pleura, which was long ago advocated by Sauerbruch and others, gives the better results. Aspiration of all the air following tight closure of the chest wall, and early and repeated aspiration of any fluid formed, is therefore indicated. The fixation of the visceral pleura to the thoracic wall by fine catgut sutures might assist in this process.

3. Pneumothorax encourages the increase and spread of pleural infection.

4. The danger from excess of pressure of pneumothorax in healthy, normal persons with normal mediastinums is by no means a matter of minor importance.

A REVIEW OF UROLOGIC SURGERY

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(Continued from page 788)

URETER

Ureteral Obstruction.—Hunner [26] finds that the presence of a stone in the ureter or kidney is presumptive evidence of coexistent ureteral stricture. Further ureteral strictures are usually bilateral and due to blood borne infection. These observations help to explain "silent" stone, renorenal reflex, calculus anuria with a stone obstructing only one side, and the development of bilateral stone. Dilatation of the stricture will often relieve the patient of symptoms even though the stone is allowed to remain. When the stricture is dilated and adequate drainage provided marked improvement in renal function will take place and in serious cases render operation safer. This is particularly the case when the stone is bilateral.

Goldstein,[27] by making a series of roentgenograms following cystoscopy and the injection of an opaque medium into the renal pelvis, made some interesting observations. After injecting the medium he removed the catheter and the usual pyelogram was made. A second plate was made in seven minutes, by which time the pelvis and the ureter should have emptied. If not, further plates are made at intervals of fifteen minutes, until they are empty. In twenty-four cases studied it was found that in obstruction of the ureter of any type there was a delay in the expelling time varying from seven minutes to four hours or more. Urinary obstruction should be studied in order to determine the amount of stasis as shown by the expelling time of injected solutions. If

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26. Hunner, G. L.: Radiographic Evidence of the Association of Ureteral Stricture and Urinary Calculi, J. Urol. **13**: 497-523 (May) 1925.

27. Goldstein, A. E.: A Study of Urinary Stasis in Ureteral Obstructions, J. Urol. **14**: 33-45 (July) 1925.

marked delay in expelling time exists, permanent ureteral catheters should be left in the ureter and renal pelvis to combat stasis and infection.

Ureteral Distention.—Gayet [28] describes a case of "forced ureter" by the mechanism of injection of a caustic substance into the bladder. He has noticed ureters which were suddenly forced or opened from below after a marked vesical contraction, and which subsequently remained open, transformed into dilated canals, establishing between bladder and pelvis a system of "vas communicans." His observation concerns a woman, aged 27, who had used iodin in order to provoke abortion; the injection had been pushed into the urethra and brought about a violent cystitis with very purulent urine. There had been no incontinence, only a slight frequency. A roentgenogram after intravesical injection of colloidal silver showed only slight distention of the bladder and extension of the solution up to the kidney pelves. These were seen to be dilated; the ureters in some areas were from 1 to 2 cm. in diameter and were irregularly dilated and constricted. Repeated lavage and internal antiseptics improved the condition of the urine. Sudden contraction of the bladder with urethral closure, penetration of urine into the ureters, subsequent infection with desquamation of the mucosa and permanent atony of the muscular coats are probably the steps followed by the process. This view seems to be in accord with the interesting experimentations of Colgate, Graves and Davidoff, reported several years ago.

Empyema of the Ureteral Stump.—Enderlen [29] reports a case of empyema of a ureteral stump in a man, aged 26. The right kidney had been removed in 1918 following trauma. In 1924 he had pain in the region of the right ureter and his urine contained pus. The stump of the right ureter was then removed; it was thickened and was as large as the small intestine. Near the bladder there was an area of narrowing similar to that in the cystic duct. Kummell was the first to call attention to this condition after nephrectomy; he reported four cases. Usually in cases in which the ureter becomes infected, a ureteral stone is present. It is only rarely that a stricture, as in Enderlen's case, causes this condition. Roedelius reported a case in which trouble occurred seventeen years later, and Brongersma a case in which empyema was present twenty-three years after nephrectomy. Usually trouble does not develop until at least a year after removal of the kidney.

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28. Gayet: Un nouveau cas d'uretéres forcés, Lyon chir. **21**:778-780, 1924.

29. Enderlen: Über das Empyema des Ureterstumpfes, Deutsch. Ztschr. f. Chir. **189**: 19-23, 1924.

PROSTATE

Control of Hemorrhage After Prostatectomy.—The difficulties of control of bleeding from the prostatic bed after prostatectomy are emphasized, and the various procedures used to control bleeding are mentioned. Ratner [30] recommends placing one tampon in the fossa on each side corresponding to the removed lateral lobe. Between these tampons a third is inserted. After thus packing the bed a gauze pack 1 mm. long by 0.5 mm. wide is introduced snugly into the rectum, thus filling up the rectal ampulla and making pressure on the prostatic bed from the rectal side. After forty-eight hours, the rectal tampon is loosened and part of it is cut away. The remainder passes spontaneously or is entirely removed by the fifth day. At the same time the bladder tampons are loosened and gradually removed so that all tampons are out by the sixth or seventh day. If the patient's general condition is good no indwelling catheter is introduced for a short time. In a large number of cases thus treated there has been no bleeding following the application of this method. The author describes a long bayonet bladed knife with which he incises the internal orifice about 1.5 cm. deep around the urethral opening, from which point digital enucleation is carried out. He feels that the procedure of enucleation is thus rendered easier.

[ED. NOTE.—Packing the rectum to control bleeding of the prostatic bed has been carried out by others. The rigidity of the rectovesical fascia and the tendency of the rectal wall to balloon out posteriorly are theoretical considerations of the method that make its practical application somewhat uncertain. The large amount of gauze needed would make one fear distention of the colon and sigmoid and much pain. However, for a period of from twenty-four to forty-eight hours, such a pack might be well tolerated and we can see no harm in using this additional measure to control bleeding from such a source. Ratner's experience covers a number of cases in which he states that he had excellent results.]

Pasteau,[31] recalling the frequency of prostatic hematuria in cases of simple hypertrophy, states that it may result fatally even without any important traumatism. In certain cases, the bleeding occurs spontaneously and may be profuse. Cystostomy performed in order to evacuate clots and leave the bladder at rest at times has not been sufficient to stop the bleeding, so that immediate prostatectomy was necessary to prevent death by hemorrhage.

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30. Ratner: Zur Blutstillung bei der suprapubischen Prostatektomie, Ein Prostatotum, Ztschr. f. urol. Chir. **17**: 101-102, 1925.

31. Pasteau: La prostatectomie d'urgence, J. d'urol. **18**: 429, 1924.

Prostatic Hypertrophy and Tuberculosis.—Legueu and Verliac [32] report the case of a man, aged 56, who had been treated a long time for stricture of the urethra. In 1915 he had a double fistula from the epididymis which suppurated for seven years. From that time on there was slight retention of cloudy and often bloody urine. In 1924, a crisis of complete retention showed the bladder filled with blood clots. Catheterism and lavage were particularly painful. Rectal examination revealed a large prostate, uniform in size and consistency. Prostatectomy was performed. The prostate contained an adenoma of the three lobes showing, on cut section of the middle lobe, three congested areas. Microscopic examination proved the tumor to be an adenoma, exhibiting also lesions of ordinary infection and of definite tuberculous alterations. The authors only found one similar case, reported in 1923 by Duvergey, but in which the prostatic tuberculosis was associated with marked pulmonary involvement. The authors are uncertain whether the hyperplasia and the tuberculosis of the epididymis, which had evolved in a latent manner during almost ten years, may have favored the early evolution of an adenoma, perhaps by irritation of the neck of the bladder. However, they add that the specific tuberculous lesions of the adenoma itself seemed to be in too early a stage to have dated from the birth of the adenoma; they believe that they would have been grafted on the growing adenoma and would be secondary to genital tuberculosis. Marion cited a similar case of his own.

Irradiation of the Hypertrophied Prostate.—In weak patients with prostatic hypertrophy radiotherapy has its place. Massive doses are employed after the major symptoms of intestinal and bladder tenesmus have been controlled for about ten days by means of vesical lavage and belladonna given internally. Massive doses seem to give better results than smaller divided doses. The symptoms remain unchanged for about fifteen days but begin to subside in about five or six weeks. In a series of cases treated by Guilbert [33] improvement has been observed. If the treatment is not satisfactory in curing the trouble, there is no obstacle to surgical treatment at a later date. In the discussion Joly recommends small repeated doses as a means of overcoming the severer types of tenesmus while Gensett recommends that the massive doses be employed only in malignant cases. The author, however, holds that larger doses are of more value in the usual cases while he reserves the smaller repeated dosage for cases in which the symptoms are so severe as to preclude the usage of any drastic form of treatment.

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32. Legueu and Verliac: Tuberculose developée sur un adenome prostatique, Société française d'urologie, J. d'urol. **19**: 441-444, 1925.

33. Guilbert, C.: Traitement de l'hypertrophie de la prostate en radiotherapie profonde, Clinique, Paris, **17**:175, 1922; abstr. Ztschr. f. urol. Chir. **16**:188, 1924.

[Ed. Note.—Death of epithelial and embryonic cells, endarteritis with vascular obliteration, and resultant cicatrization are the effects of radiotherapy. It would be interesting to study the effect of radium and roentgenologic treatment in the cases in which the hypertrophic prostate is made up of softer parenchymatous elements and those in which the fibrous tissue predominates. The end-results in such a series might afford some clue to the reason why we see such conflicting reports in the result of radiotherapy. At the present time we may consider that the deep roentgenologic treatment of prostatic hypertrophy is still experimental. A few brilliant results, however, are reported from time to time and it is these that render the continuance of the experiment, especially in cases unsuited for operation, not only justifiable but commendable.]

Kogan [34] reports a series of cases of retention due to prostatic hypertrophy in which operation could not be performed or had to be postponed. Intrarectal and intra-urethral applications of radium led to recovery in three cases, marked improvement in one for three years, and incomplete results in two. In two of the cases the prostate was removed after radium treatment, and Marion, who operated on them, encountered no more difficulty in his extirpations than he would have if no treatment had been given. It might be advisable to submit inoperable cases, in which frequent catheterism is necessary, to radium treatment in order to improve the condition. Usually improvement will be noticed; aggravation will never take place, and unfavorable conditions for further surgical intervention will not be created.

Cancer of the Prostate.—Gayet [35] is not opposed to the use of radium in cancer of the prostate. He states that operation is often without benefit and that radium may be a great help, decreasing hemorrhages, causing a diminution in the volume of the gland, and sometimes aiding the return to function of a previously obstructed urethra. Gayet states that accidents occur from the use of radium. One patient with a cancerous prostate which was still localized was treated with radium; the tubes were placed in the depths of the tumor, the gland was small and the rays affected the small intestine in the pouch of Douglas causing serious lesions which were followed by adhesions, subsequent angulation and intestinal obstruction; these lesions in certain areas almost perforated. This was ascertained at operation. The patient died. The tumor was small and Gayet believes that, on account of this, the intestine had not been sufficiently protected from the rays. Similar cases have been reported before. A means of protecting the organs situated in the pouch

34. Kogan: Hypertrophie de la prostate et radium, J. d'urol. **19**:23-29, 1925.

35. Gayet: Quelques dangers des applications de radium pour cancer de la prostate, Lyon chir. **21**: 576-579, 1924.

of Douglas should be provided. Gayet has also had two cases of venous thrombosis in the treatment of prostatic cancer with radium; one of them was followed by death due to embolism and the other by bilateral phlebitis in the lower limbs.

Sarcoma of the Prostate.—Culver [36] finds twenty-five cases of sarcoma of the prostate in the literature and adds one, which he reports in detail. This disease is most common in the very young and in the adolescent, but may occur at any age. Metastasis is relatively rare, considering the large size and rapid growth of the primary disease. Metastasis, when it does occur, is usually by the blood stream. When present, the symptoms are those associated with vesical or rectal obstruction. The first symptom in the young is frequently acute urinary retention, which may have been preceded for a few days by dysuria and frequency. In adults the progress of the disease is frequently less rapid. Hematuria is not common. The results of treatment are uniformly unsuccessful. Culver's patient was a boy, aged 12 years, who developed a cauliflower-like mass at the site of extraction ten days after the removal of a tooth. About the time of the extraction of the tooth he began to have suprapubic pain associated with dysuria and frequency. Two days after, acute retention followed. There was a large soft mass replacing the prostate. No nodular areas were felt, but the mass was not of the same consistency over its entire posterior surface, there being small isolated areas definitely softer than the remainder of the growth. The right seminal vesicle was palpable and nodular, being firmer than any part of the prostatic mass. Cystoscopic examination revealed a greatly elevated trigon, which was continuous with an intravesical protrusion of the growth. Because of inability to catheterize further, suprapubic cystotomy was performed and the growth enucleated. The patient died on the twenty-second day after operation with bronchopneumonia, pyelonephritis and local recurrence.

Prostatic Cysts.—After a careful review of the literature of cysts of the urethra and of the prostate, Wesson [37] concludes that such cysts are not nearly so rare as is generally supposed. Fifty-five cases are reported in the literature; of these twenty-nine were cysts of the prostate. In addition, four new cases of prostatic cysts are reported.

Cysts are found throughout the course of the urethra in both sexes. In the male it is generally considered that the cysts of the anterior urethra arise from the glands of Littré while those of the prostate, vesical orifice and posterior urethra originate in the prostatic tubules. The

36. Culver, H.: Sarcoma of the Prostate, J. Urol. **14**: 47-55 (July) 1925.

37. Wesson, M. B.: Cysts of the Prostate and Urethra, J. Urol. **13**:605-632 (June) 1925.

homologue of the prostate in a woman being Skene's glands and the urethral glands, cysts may occur anywhere in the course of the female urethra.

Inflammatory excrescences and lymphocystic lesions of the vesical orifice may easily be mistaken for cysts or polyps, while cysts having thick walls situated in this area are usually confused with an Albarran's lobe.

The symptoms of cysts of the prostate vary from being quite negligible to definite interference with urination, depending on the size and the site of the tumor. Wesson states that retention of urine of sudden onset in a man under 50 years of age, which is relieved by the passage of a sound or catheter, is indicative of a cyst. Small cysts situated in the posterior urethra or on the verumontanum give rise to symptoms of posterior urethritis.

Treatment depends on the site and the nature of the cyst. In the majority of cases, fulguration through a cystoscope or urethroscope is the method of choice. Sessile cysts may be ruptured and their bases fulgurized with good results.

Prostatectomy and Potentia.—Lieschied [38] discusses the influence of prostatectomy on the libido. The analogy of hypertrophy of the prostate to myoma of the uterus suggests that the former may be a process associated with a sort of male climacteric. The age of the patient, the general condition before and after operation and the preoperative and postoperative libido are definitely related. Lieschied reports several series of cases to show that total prostatectomy after the method of Voelker has no unfavorable influence on sexual potency. Injury to the perineal nerves may affect sphincter function, and injury to the prostatic plexus of nerves is to some extent necessary in the operation. However, it has beeen shown experimentally in dogs that prostatectomy associated with such lesions causes little or no interference with sex functions. The clinical results studied by Lieschied tend to bear out the fact that ischiorectal prostatectomy does not influence sex function unfavorably.

[Ed. Note.—Because of the nature of the question, clinical data of this type are hard to accumulate and conclusions more difficult to determine. It is probably the impression of most surgeons who have frequently performed prostatectomy that their operations have not interfered much with the sexual potency of the patient. Nature and age have usually done that before the operation is indicated. It is remarkable to see as we do some patients retain their complete sexual vigor after prostatectomy. Yet the prostate has no internal secretion so

38. Lieschied, Alfred: Zur Potenzrage nach der Voelckerschen Methode der Prostatektomie, Ztschr. f. urol. Chir. **16**: 151-154, 1924.

far as scientific endocrinology has been able to show, certainly none which is associated directly with the libido. Secondary effects, such as a relation between the prostatectomy and atrophy of the interstitial cell, are much discussed among experimenters in this field, and reports are conflicting. Probably the effect of prostatectomy on the testis is only slight.]

BLADDER

Bilharzia Infection of the Bladder.—Felix [39] examined the urine of fifty-three children from the Palestine Orphanage. Twenty-three children (43 per cent.) were found to be infected with *Schistosoma haematobium.* The majority of the children had no pain and no difficulty in urinating. Similar observations were made in another locality in the neighborhood of Jaffa. The result showed that, out of a total of 158 boys from 14 to 18 years of age, twenty-one (13.3 per cent.) were infected. Clinical symptoms were again markedly absent in these cases. The diagnosis in light cases is at times quite difficult to make. Repeated microscopic examinations are often required before a decision can be reached. Bilharzia eggs are often found after a succession of earlier examinations has produced negative results. In other districts, particularly in Egypt, infections of bilharzia are much higher. Fergusson found in 1913 that 62 per cent. of a group of Egyptians were infected with one or both forms of bilharzia; Madden states that 10 per cent. of these patients died as a result of the disease or its complications. In 1917 Boulenger found up to 29 per cent. of the male Arab population to be infected. In examining specimens of urine for eggs, Felix lays emphasis on the necessity for collecting the last drops separately. In spite of the consistent and careful technic followed in the examination of patients with bilharziasis, the microscopic examination of the urinary sediment often gives a negative result. Not only are bilharzia eggs not found, but the sediment may often be completely free from blood cells.

Hematuria usually appears periodically. Kartulis states that it appears fortnightly in most cases and continues for a few days. Eosinophilia is not a constant symptom of schistosomiasis. In forty-one cases showing bilharzia eggs in the urinary sediment the differential leukocytic count revealed only ten cases in which the eosinophils were as high as 4 per cent.; that is 24.5 per cent. of bilharziasis cases showed normal percentages of eosinophil cells. In patients infected with bilharzia there are usually other conditions, such as those caused by intestinal parasites, which tend to produce eosinophilia. The complement fixation test with the patient's serum was positive in about 80 per cent. of these cases. Fairley states that the use of antimony absolutely ensures success in the

39. Felix, A.: Observations on Vesical Bilharziasis in Palestine, Am. J. Trop. Med. **5**: 41-61 (Jan.) 1925.

treatment of bilharzia; the ova disappear from the urine, urinary symptoms and eosinophilia cease, and the positive complement fixation test gradually disappears. The constant efficacy of antimony rests on its direct specific action on the parasites. In contrast to the antimony treatment Tsykalas reports 200 cases in 90 per cent. of which intravenous injections of emetin produced complete and permanent cure. Cawston finds that in combating bilharziasis in children and young people, intramuscular injections of emetin are more effective than intravenous injections of antimony. Felix obtained excellent results with the intravenous injections of antimonium tartrate. In the application of the large doses he did not have a failure in forty-one cases. After the first three to five injections the hematuria ceased, even in those cases of old hematuria periodica. After total injections of from 0.3 to 0.5 gm. there were no bilharzia ova in the urinary sediment. Felix's experiences with subcutaneous injections of emetin hydrochlorid were entirely unsatisfactory. He states that a transitory improvement was produced in all the cases; hematuria ceased and ova disappeared from the sediment during the period of the treatment and for a few weeks after its close. After that, however, there was a relapse in each case, without exception.

Cases of infection of the bladder with *Schistosoma hematobium* are comparatively rare in this country. Schwarzwald has demonstrated that a snail of the bullinus type serves as an intermediary host for the urinary schistosoma. A type of planorbis is considered as the intermediary host for the intestinal variety. Werner of the Zoological Institute of Vienna states that planorbis occurs in all of Europe while bullinus is not found in Europe. Schwarzwald [40] reports a case of urinary bilharziasis. The patient, a young man, was born in Galatia, and moved to Palestine in 1920. In 1922 he noticed for the first time that after micturition there was a terminal drop of blood. There followed attacks of weakness; from January, 1923, he noticed regularly several drops of blood after micturition. This gradually increased to a regular hematuria. The urine contained red blood cells and the characteristic ova of *Schistosoma hematobium*. Cystoscopic examination showed marked changes of the mucous membrane of the bladder: at the trigonum, especially on the right side, there was a group of beetlike projecting plaques covered with a dull red mucous membrane and studded with a series of opaque light yellow nodules 1 mm. in length; each of these was surrounded by a red area. One of the beetlike infiltrations showed, beside these opaque stipplings on the one side, on the other a close group of vesicles 1 mm. in diameter.

40. Schwarzwald, R. T.: Ein Fall von Bilharzia-Erkrankung der Blase, Ztschr. f. urol. Chir. **16**: 117-120, 1924.

Of the remedies for bilharziasis the most prominent are antimonium tartrate, recommended by Christopher in 1918, and emetin, for whose use in treatment Tsykalas asserts priority (1913). Antimony and emetin, if much used in the treatment of bilharziasis, are at times toxic. The alkaloid of ipecacuanha supersedes antimonium chlorid in the intensity and rapidity of its sterilizing effect; the latter destroys the viability of the embryo on the ninth or tenth day, the total destruction taking about twenty-eight days; while with emetin the viability of the embryo is destroyed as early as the fourth or fifth day of treatment, and total destruction is accomplished after ten or twelve days. Emetin occasionally causes various neurotrophic conditions and at times ulcerative stomatitis; on the other hand favorable results have been obtained by Day with the use of antimony and potassium tartrate (tartar emetic), which is inexpensive and readily obtained.

In Schwarzwald's case antimonium tartrate was given intravenously on twelve consecutive days: 0.003 gm. dissolved in 2 c.c. of water was injected on the first day; 0.06 gm. on the second day, and 0.1 gm. in each of the doses from the third to the twelfth day. The bleeding had occurred for the last time a week before the beginning of the treatment; once after the sixth injection there was strangury and burning on urination, lasting several hours. After the second injection, the cystoscopic picture was surprisingly more favorable; the swelling had gone down, the plaques were flatter; the redness and infiltration as well as the vesicles had almost disappeared. The nodules remained unchanged. After a week (following the ninth injection) the change in the bladder picture was striking. The infiltration had disappeared entirely, and in its place there was only a striated and spotted redness of the mucous membrane which otherwise seemed about normal. The miliary nodules seemed less in number, appearing more grayish white, but otherwise had not changed. The cystoscopic examinations after the completion of the treatment showed an absolutely normal condition with the exception of the persisting grayish white nodules. The patient is considered cured, the cure having been effected by the use of antimonium tartrate in twelve days.

[ED. NOTE.—Hager of the University of Wisconsin has had an extensive experience in the treatment of schistosomiasis in Santo Domingo. He states that the species of schistosoma that are pathogenic for man are divided into four groups depending on their localization and are therefore designated as liver flukes, intestinal flukes, lung flukes, and blood flukes. Of these four, the blood flukes which include *Schistosoma hematobium, Schistosoma mansoni* and *Schistosoma japonicum* are of foremost importance because of their pathogenesis and rather extensive distribution in the tropical and subtropical regions. From the stand-

point of the genito-urinary surgeon, *Schistosma hematobium* is of considerable importance for it is the type that has predilection for the bladder and adnexa producing a cystitis of a variable degree, with involvement of the prostate and seminal vesicles as well as fistulous destruction of the penis and of the perineum. Various observers have suggested that the parasitic trematodes of man are capable of carrying on their development in a variety of fresh water mollusk. It is estimated that there are some twenty species of snails that are known to be carriers of the human schistosomes, nine of which are credited with being the intermediate host for *Schistosoma hematobium.* It is in the mollusks of the families panorbidae and limaeidae that the western form of schistosomiasis usually develops. The genera of these forms are widely distributed throughout the western hemisphere and Europe. Some of these snails are capable of harboring the cercaria of both *Schistosoma hematobium* and *Schistosoma mansoni.* In 1903 Sir Patrick Manson found lateral spined eggs in a patient from Antigua in the West Indies who was suffering from rectal symptoms and associated the disease with schistosoma. Numerous reports have since been made concerning the presence of rectal bilharziasis in Porto Rico. Yet in Santo Domingo, one of the neighboring islands of the West Indies, an authentic report of the presence of the disease had not been made until the spring of 1923, when Profillo of Santo Domingo City reported a bona fide case of intestinal schistosomiasis. Hager found one case in Santo Domingo City in 1921. It occurred in an American who had formerly lived in Haiti and Porto Rico and who was suffering from an obscure form of dysentery. Just how much concern the possibility of an increase in the distribution of fluke infections should cause remains to be seen. Apparently when we possess the hosts that are essential to complete the cycles of development there is a potential danger of an epidemic. In Egypt, with a population of between 13,000,000 and 14,000,000, 11,000,000 are affected with bilharziasis. Approximately 500,000 persons die annually of the disease. It is apparent that the disease which has been a scourge in Egypt since ancient times is still rampant and continues to be of prime economic importance. Sporadic cases have been reported from several of the European centers. A number of cases have been under observation by American urologists even among persons who have never lived in regions where the disease is endemic. One of the essentials in the complex etiology of schistosomiasis is the necessity for an intermediate host, such as the snail, which permits the flukes to undergo a profound metamorphosis before they can attack man. The range of distribution of the disease is therefore limited by a suitable intermediary host, and it seems probable that the distribution of an appropriate host is much greater than we had previously sup-

posed. It is this factor, in the light of recent investigations, that revives the question as to the extent to which diseases common to the tropics may become cosmopolitan.]

Tumor of the Bladder.—Smith [41] reports the case of a man, aged 33, who complained of acute retention with pain. He had had some frequency of urination for ten weeks. For several weeks there had been terminal burning, and an occasional speck of blood had been passed. For three weeks there had been complete retention. On cystoscopy a large vesical tumor, involving the right wall of the bladder, the trigon and both ureteral orifices, was found. It had a broad base and bled easily. At a second cystoscopic examination a small piece of the tumor was removed for microscopic examination. This was reported to be a round cell sarcoma. Suprapubic drainage was instituted; the tumor grew rapidly and soon protruded through the drainage opening. Roentgenologic treatment was of no avail. The patient died in four months and at that time necropsy showed a sarcoma of the bladder with generalized metastasis, chronic cystitis and bilateral pyonephrosis. Sarcomas of the bladder are unusual. Smith states that they occur in from about 4 to 5 per cent. of bladder tumors. Though they are more common in children and in old people they may occur at any age. Metastasis is brought about by the blood stream. There are no distinguishing symptoms or findings to differentiate sarcoma from other vesical tumors before pathologic examination is made. In this case the disease was particularly resistant to roentgenologic treatment. The prognosis always is poor.

[Ed. Note.—Sarcomas, like other connective tissue tumors of the bladder, occur earlier in life than epithelial tumors. They are exceptionally rare and extremely malignant. Smith's figures showing that they comprise from 4 to 5 per cent. of all bladder tumors are higher than one usually sees. There was only one sarcoma in 333 cases of tumor of the bladder operated on at the Mayo Clinic between January, 1910, and January, 1920. Undoubtedly some of the cases reported as sarcoma are not sarcoma. Fenwick cites a case from Guy's Hospital which had been diagnosed as round cell sarcoma. Targett reexamined the specimen and found it to be merely round cell infiltration in a fibropapilloma.]

Hunt [42] believes that improvement in the results of treatment of malignant tumors of the bladder requires acceptance of the present day knowledge of the character of the lesion, the standardization of treat-

41. Smith, E. C.: Primary Sarcoma of the Bladder, Canad. M. A. J. **15**: 628-630 (June) 1925.

42. Hunt, V. C.: Disposal of the Ureter in Surgical Excision of Malignant Tumors of the Bladder, J. Urol. **14**:19-31 (July) 1925.

ment, and its application early in the disease. To discuss satisfactorily the results of treatment in these cases the degree of malignancy must be considered.

The determination of the grade of malignancy of a given tumor of the bladder, by the examination of a specimen removed through the cystoscope, serves as an excellent guide to the surgical procedure. The ultimately poor results obtained from any and all methods of treatment of tumors of high degree of malignancy lead to conservatism in the radical excision rather than to readiness to subject the patient to high risk with little prospect of cure. On the other hand, in cases of local extensive involvement from a tumor graded 1 or 2, the risk of wide excision by radical operation is justified because of the better prognosis. Thus, the use of this method of preoperative grading of the degree of malignancy offers a means of deciding on the merit of radical operation for a given tumor. Neoplasms of the bladder usually are highly malignant. In 393 of the series of 553 cases of malignant neoplasms of the bladder observed at the Mayo Clinic, including those in which the disease was so extensive that treatment was not attempted and in cases in which treatment by fulguration, radium or operation was given, the degree of malignancy was determined by Broder's method. Fifteen and one-half per cent. were graded 1; 32.8 per cent., 2; 32.5 per cent., 3, and 19 per cent., 4. This should represent the relative incidence of all malignant tumors of the bladder irrespective of size, extent of involvement or classification on a therapeutic basis.

The relatively better end-results obtained by surgical excision of the low grade malignant tumors, and the infrequency of recurrence, against the 35 per cent. of recurrence following nonsurgical therapeutic measures, warrant the continuance of surgical extirpation in these cases. However, the choice of surgical excision of tumors graded 3 and 4 must be based on their size and situation, with particular reference to involvement of the ureter and the associated risk of the procedure. Few therapeutic procedures justify their application when the attendant risk exceeds the prospects of benefit or cure. Likewise, any therapeutic procedure curative in purpose should offer greater length of life and more comfort than no treatment.

In cases of large resectable malignant tumors of the bladder, in which the ureter is involved, occluded or encroached on, it is necessary to divide the ureter and dispose of it subsequently either by ligation, placing entire reliance for total renal function on the remaining kidney, or by transplantation of it into a new segment of the bladder.

From January 1, 1910, to January 1, 1925, ninety-eight segmental resections of the bladder with ligation or transplantation of the ureter were performed at the Mayo Clinic for malignant tumors. Seventy-two

of these tumors were graded: 8.3 per cent. were Grade 1; 20.8 per cent. were Grade 2; 47.2 per cent. were Grade 3, and 23.6 per cent. were Grade 4. In forty-five cases the ureter was disposed of by ligation, with six postoperative deaths, a mortality rate of 13.3 per cent. While clinical causes of death were general sepsis, pneumonia and empyema, necropsy disclosed acute pyelonephritis in all.

In fifty-three cases the ureter was disposed of by transplantation, with sixteen deaths, a mortality rate of 30.1 per cent. Deaths occurred from the third to the fifty-sixth day after operation. The clinical cause of death in each instance was ascending infection; this was confirmed by necropsy in eleven cases.

The merit of any surgical procedure must be based on its attendant risk, mortality rate and ultimate result. So far as ultimate results are concerned after radical excision of a malignant tumor of the bladder by either method of disposal of the ureter, a review of the incidence of recurrence leaves little to choose. However, experience with transplantation of the ureter, with its resultant mortality rate of 30 per cent., does not justify its choice over the procedure of ligation of the ureter, with a mortality rate of 13.3 per cent. and with equally good ultimate results. Even though nephrectomy was necessary in two cases and drainage of an infected hydronephrotic sac was called for in three cases following ureteral ligation, the danger from such conditions and procedures does not compare with those from ascending infection, which is so prone to follow transplantation.

Vesical Stone.—Meyer [43] states that the unsuccessful attempts made to dissolve vesical calculi were usually due to too weak solutions of acid and insufficient duration of contact. He reports two cases. The first patient exhibited marked cystitis, following cystostomy, consequent on a rupture of the urethra. The roentgenograms showed three calculi in the bladder, each about 1 cm. in diameter. Gradually increasing solutions of hydrochloric acid (from 0.6 to three parts of hydrochloric acid to 1,000 parts of water) were used without interruption for a period of nine days, at the rate of 10 liters a day, after which no trace of stone could be found. Subsequent suture of the urethra completed the cure. The second patient was aged 82 and weak. He had a large vesical stone, 5 cm. in diameter, estimated to weigh about 30 gm. Continuous injection, as described, was carried out for six days. He died a little later of bronchopneumonia; at necropsy the stone was found to be reduced to a small shell 1 by 2 cm. and weighing only 1.15 gm.

43. Meyer, Johannes: Sur la dissolution des calculs vesicaux et le traitement consecutif aux operations sur la vessie et l'urètre, Presse méd. **33**:187-188 (Feb. 11) 1925.

Diverticulum of the Bladder.—Read,[44] in reviewing the cause of infection and symptoms in vesical diverticula, is of the opinion that obstruction plays an important part. The only cure is radical excision. Even when radical excision is performed it is essential that the obstruction be relieved. In cases in which radical treatment is inadvisable very satisfactory results may be obtained by palliative means. The conservative treatment consists of, first, removing the obstruction to the free passage of urine (prostate, median bar, stricture and so forth) and, second, the dilation of the mouth of the diverticulum, and attempts to prevent its recontraction. Through a suprapubic incision, free exposure of the diverticulum is secured. Its mouth is thoroughly dilated with the fingers. This fibrous ring is then grasped with artery clamps and put on the stretch. With the radiotherm cautery knife the fibrous ring is incised completely through its thickness. These incisions are made in three or four places. This must be done delicately, but deliberately, until the fibrous ring is completely severed. A good exposure is necessary since inspection, as well as palpation, is needed to avoid carrying the incisions too deeply. Results carefully observed in two cases in which this procedure had been followed indicate that there is a free communication between the sac and the true bladder. In one case the residual urine, as measured nine months after operation, had been reduced from 6 ounces to 0.5 ounce; in the other, from 24 ounces to 0.5 ounce, though in the latter case much of the residual urine was due to obstruction in the bladder itself.

Habit Bladders.—Pelouze[45] described the results and cystoscopic pictures found in patients who have developed abnormal habits in connection with urination. The commonest type is the pseudo-atonic bladder. This type is seen in those people who from false modesty or other reasons make it a practice to hold their urine for prolonged periods. The result of this habit is a large, pale, apparently thin walled viscus. Its tolerance to cystoscopy and the fact that it usually shows fine muscle band tracings are prone to raise the question of lesion of the spinal cord. One should not be misled in this regard, as the reflexes are normal and a history of the habit so easily obtained. They give no symptoms and are found because other conditions have indicated cystoscopy.

The opposite of this condition is seen in hypersensitive and neurotic people who empty their bladders at the slightest suggestion of desire; this habit the author terms habit pseudocontracture. Cystoscopically such bladders are usually erroneously classed among the abnormally

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44. Read, J. S.: A Palliative Treatment of Bladder Diverticula, J. Urol. **13**: 537-544 (May) 1925.

45. Pelouze, P. S.: Habit Bladders; Discussion of Medical and Surgical Aspects of Effects of Habits on Urinary Bladder, J. Urol. **13**:679-687 (June) 1925.

small bladders as they seem to hold only a small quantity of fluid. The mucosa is normal throughout, except at the trigon where it is reddened. The trigon and posterior urethra are hyperesthetic.

Habit trabeculation is the result of habitual straining to hasten urination; here the picture resembles that seen in prostatic obstruction. In this relation might also be mentioned a vesical picture of marked trigonal injection in women in the absence of any pelvic or urogenital lesion. Its annoying symptom is great frequency of urination. The author has been able on several occasions to associate this with excessive sexual indulgence and, on two occasions, observed it in unmarried women exhibiting the prudery and vulvar appearances commonly attributed to digital masturbation.

Regurgitation of Vesical Contents.—Graves and Davidoff [46] find that regurgitation of vesical contents into the ureters may be readily observed, experimentally, in normal animals. This phenomenon, in rabbits, cats and dogs, depends primarily on sustained tonus of the vesical musculature as it actively resists distention. Reflux never occurs in those cases in which this active sustained resistance is lacking, either through an inherently depressed state of the muscle fibers at a given time, or through a depression produced by external agents, such as extremes of temperature or strong chemicals.

The oblique ureterovesical junction, with the resulting valvelike arrangement, which has always been proclaimed as an efficient safeguard against regurgitation, has beeen proved, experimentally, to be insufficient protection against the ascent of the accumulating contents of the bladder into the ureters in the presence of an actively contracting bladder with obstruction of the vesical neck.

Because in a series of experiments in which the ureters had been rendered inactive or abnormal, reflux occurred just as frequently as with normal structures, the authors conclude that the degree of ureteral activity has relatively little bearing on regurgitation. They have never seen antiperistalsis in a normal ureter and in no way have they found it concerned with regurgitation.

The lesser incidence of regurgitation in dogs as compared with rabbits and cats is due, not to difference in the structure of the ureterovesical junction, as has been previously supposed, nor to a lack of tone of the vesical musculature, but to the failure of the bladder contractions to be sustained in the presence of continually increasing distention.

The belief of the authors, based on these studies, is that regurgitation from the bladder into the ureters may be accountable for ascending

46. Graves, R. C., and Davidoff, L. M.: III, Studies on the Bladder and Ureters with Especial Reference to Regurgitation of the Vesical Contents; Regurgitation as Observed in Cats and Dogs, J. Urol. **14**:1-17 (July) 1925.

infections of the urinary tract, particularly in cases of obstruction of the vesical neck.

Residual Urine in Women.—Curtis [47] states that residual urine occurs not only in association with cystocele, in the puerperium and after operation, but that it frequently occurs during the course of pregnancy and may result from habitual distention of the healthy bladder. After operation the use of the catheter should be avoided when possible, but no patient should be allowed to suffer from distention. Provided the catheter has not been required, the presence of some residual urine for a few days is not a particular menace. Patients who require repeated catheterization almost invariably fail to recover immediately the power of complete evacuation on resumption of spontaneous micturition. The daily withdrawal of residual urine until function becomes normal gives good results and affords excellent prophylaxis against infection of the urinary tract. Catheterization, immediately after urination, preferably with lavage, should be repeated daily until residual urine disappears.

Cancer of the Urethra.—Christen [48] reviews eight published cases of urethral cancer and adds to them one of his own. He states that primary carcinoma of the male urethra is a rare disease usually occurring in patients about 50 years of age. Its etiology is obscure; gonorrhea seems to be the most frequent predisposing cause. The pathologic appearance of the tumor is usually that of a stratified epithelioma. Three periods constitute the steps of the disease: a slow insidious onset with tumefaction and signs of stenosis; later, the growth extends with ulceration, fistulas and hemorrhages; finally, urinary infection sets in, the tumor becomes generalized and death occurs in a state of cachexia. The prognosis is always bad, although in a case reported by Scholl and Braasch the patient was still living six years after operation. Treatment should be surgical; it may bring about a cure, especially if the diagnosis has been made early and if the tumor occurs in the glans. Recurrence is the rule. Operative procedure consists in amputation through healthy tissue, emasculation and extirpation of the regional lymph nodes. Postoperative treatment with radium or roentgen ray is advisable.

[ED. NOTE.—Primary carcinoma of the male urethra is extremely rare. In a series of 16,637 cases of tumors of various organs reviewed by Gurlt from Vienna clinics, no instance of malignant growth of the urethra was noted. At times urethral carcinomas are preceded by long periods of urinary difficulty and irritation. There is a gradual

47. Curtis, Arthur: Residual Urine in Women, Surg., Gynec. & Obst. **40**:689-670 (May) 1925.

48. Christen, R.: Etude sur le cancer primitif de l'urètre chez l'homme, J. d'urol. **19**:304-315 (April) 1925.

metaplasia of the epithelial lining of the urethra to a condition resembling that of skin which may go on to the formation of an epidermoid carcinoma. König reported a case of urethral carcinoma developing after urinary obstruction of forty-eight years' duration, and Oberlander noted a somewhat similar case developing after forty years of urinary difficulty. Traumatic stricture in some cases has the same malignant potentialities as those of infectious origin. In one case reported by Witsenhausen the stricture persisted thirty-eight years before malignant changes occurred. In the majority of cases the carcinoma occurs at the usual site of stricture in the cavernous and membranous urethra. Of forty-two cases of carcinoma of the male urethra reviewed by Preiswerk, thirty-eight were in the membranous or cavernous urethra. Most of these tumors are squamous cell growths. They are highly malignant although they tend to remain limited to the local area and to the regional lymph nodes.]

Urethral Valve Formation.—Bumpus [49] reports the case of a man, aged 62, for whom suprapubic prostatectomy had been performed two years before; complete incontinence resulted, and he was obliged to wear a rubber urinal. This, by infringing on the distal portion of the urethra, frequently resulted in distention of the remainder of the urethra with the obstructed urine, until a change in the position of the urinal permitted the urine to escape. After approximately six months the patient discovered that even when the urinal was removed the point of pressure on the anterior urethra tended to act as a valve, and resulted in the temporary retention of urine in the remainder of the urethra. The proximal portion of the urethra gradually dilated and assumed the shape of a pouch. As this pouch became more distended, the distal portion of the urethra that was not included folded over on itself, thus forming a valve. The more distended the urethra the tighter the valve became and the more perfect the valvular action. As a result the patient had been able to discard the urinal. As soon as the bladder filled, the urine flowed into the urethral sac, which was capable of holding several ounces. When this became distended the patient emptied both urethra and bladder immediately by inserting a short length of catheter about 3 or 4 cm. beyond the valve.

Urethral Stricture.—Stricture of the urethra should be diagnosed before definite signs of obstruction occur. Attwater [50] points out that the bladder is disturbed in its function as soon as urethral infiltration is established, and that the disturbance becomes greater as the degree of

49. Bumpus, H. C., Jr.: Unusual Dilatation of the Urethra with Valve Formation, J. Urol. **13**:551-553 (May) 1925.

50. Attwater, H. L.: The Importance of the Early Recognition of Urethral Strictures of Large Caliber, Practitioner **114**:357-361 (May) 1925.

stricture formation increases. With more work thrown on the bladder, changes soon take place in the kidneys and ureters. The importance of this needs no comment. Attwater uses the air dilation urethroscope and the Kollmann dilator for diagnosis and treatment of the condition.

[ED. NOTE.—One must agree with the author on the importance of early diagnosis of stricture but one cannot concur in his advice that an air dilating urethroscope and Kollmann dilator are the only essential instruments in diagnosis and in treatment. To omit the use of bulbous bougies in diagnosis and steel sounds in treatment would appear to be unwise. We often need all means at our disposal in these cases. The danger from air embolism accompanying the use of the air dilating urethroscope must be borne in mind.]

Urethral Prolapse.—Watkins [51] states that urethral displacements or urethroceles are almost solely due to the traumatism of labor. The tension on the fascia which causes the lesion is chiefly produced by downward pressure of the fetal head on the cervix, or by the traction in forced delivery. Senile atrophy and infection are prominent factors in prolapse of the mucosa. Urinary incontinence, mechanical disturbance associated with protrusion and irritability of the bladder due to chronic infection are the chief symptoms. Uncomplicated urethrocele is rarely seen, and is usually associated with cystocele. The treatment is entirely operative. Important features in the operative repair are free mobilization at the chief site of retraction, transverse suture at the site of injury of the vesicovaginal fascia so that the sag of the urethra will be corrected, and care in bringing firm tissue together over the base of the urethra. Failure to obtain satisfactory urinary control is due to errors of judgment or defective technic rather than to the absence of tissue. The probability of cure should be excellent as strong fascial tissues can be utilized.

Urinary Infection.—Sanguinetti [52] briefly reviews the controversy as to whether pyelitis has its orgin from ascending or hematogenous infection. He seems to favor the theory of ascending infection. He recommends treatment by instilling from 2 to 3 ounces of 0.5 per cent. colloidal silver into the bladder through a soft rubber catheter. He reports a series of seventeen cases of urinary infection in which the following varieties of bacteria were found: staphylococci only in two cases; *Bacillus coli* and streptococci in two cases; *Bacillus coli* and staphylococci in two cases; *Bacillus coli* only in eleven cases. Cure

51. Watkins, T. J.: Prolapse of the Female Urethra, Surg., Gynec. & Obst. **40**:687-689 (May) 1925.

52. Sanguinetti, H. H.: Urinary Infections with B. Coli and the Pyogenic Cocci; Their Pathology and Their Treatment with Collargol, Brit. M. J. **1**:1168-1170 (June 27) 1925.

was obtained in eleven cases, in the sense that at the end of treatment neither pus nor bacteria were present in the urine, as proved by microscopic and cultural tests. In seven of these the urine was known to have remained sterile for at least a month. It was not possible to keep the remaining four patients under observation as long. In the fourth case in the series the patient had had three attacks, each of which had been successfully dealt with, the urine having been rendered sterile on each occasion for lengthy periods. There had, then, been a successful result in 64.7 per cent. of the cases, or, if the fourth case is counted, in 68.4 per cent. Unless treatment is continued until the urine is free from pus and sterile, relapse is likely to occur. Macroscopic examination certainly is not sufficient, nor does the author think we may be content with microscopic examination. Cultural tests are almost essential, although, in the case of infection with *Bacillus coli* or streptococci, the development of three or four colonies of *Staphylococcus albus* on the culture medium may indicate no more than infection from external parts during the passage of the catheter.

[ED. NOTE.—In view of the generally recognized acceptance of the theory of hematogenous origin of urinary infections with *Bacillus coli* and other organisms one may be doubtful of the benefit of treatment applied to the bladder only. In the cases reported cystoscopic examination was not made and they cannot therefore be accepted as cases of definite renal infection.]

Young [53] reviews his past work on the use of mercurochrome and records seventy-six cases in which it has been used intravenously. He recommends the use of a 1 per cent. solution made up with freshly distilled water from the granular form of mercurochrome-220 soluble. An average dose is 5 mg. for each kilogram of body weight; this amounts to 22.5 c.c. of a 1 per cent. solution for 100 pounds (45.4 kg.) of body weight. A few instances are recorded in which doses of 7 and even 8 mg. for each kilogram were used. In some instances the dose was much smaller, and Young believes that in many instances the poor results obtained may be directly due to insufficient dosage.

In rare instances 5 mg. or more for each kilogram have been followed by little or no reaction, but in most cases there is a definite and often pronounced reaction, consisting of an immediate slight depression, a feeling of discomfort in the upper part of the abdomen and perhaps a slight headache, followed shortly afterward by nausea, slight or pronounced, and a little later by bowel movements, which, however, are often absent. In febrile cases there is a rise in temperature, varying from 1 to 5 degrees, which usually comes on within from three to four

53. Young, H. H.: Intravenous Mercurochrome in the Treatment of Urological Infections, J. Urol. **13**:633-672 (June) 1925.

hours after the injection. In some cases this is accompanied by a chill which is rarely severe. In one case a rise in temperature to 107.5 degrees was recorded and the patient recovered. The initial rise in temperature is almost always followed by an early and profound drop, not infrequently to normal or nearly so. In rare instances there is a fairly profound shock following the injection and cases are recorded in which the pulse has become bad, the patient cold and clammy and the shock so severe that restoratives were immediately required.

While no definite statements can yet be made as to the nature of these febrile reactions or their importance in a cure, it is the author's impression that in those cases in which a pronounced febrile reaction occurs, a favorable response and ultimate sterilization after intravenous injections of mercurochrome-220 soluble are much more likely to follow.

The gastro-intestinal reactions are often very annoying and sometimes acutely distressing but they rarely last more than twenty-four hours, and in the author's long series of compiled cases no evidence of any permanent injury has been found. Stomatitis is a much rarer complication and was only occasionally more than slight. In a few recorded cases a pronounced stomatitis occurred, and in one of the cases the patient suffered a good deal for about one week. Here, again, the reaction was never dangerous or permanent in its effects.

While there were many failures in the seventy-six genito-urinary cases recorded in which mercurochrome-220 soluble had been used, and in others only slight improvement, particularly in acute simple gonorrhea, nevertheless the author believes that the undoubtedly good results obtained in the great majority of cases cited are sufficient to warrant an extended use of this new form of therapy in urology. In acute infections of the genito-urinary tract associated with high fever, the most pronounced results were obtained, both in infections due to the cocci and the bacilli. In chronic afebrile infections of the urinary tract, particularly those due to *Bacillus coli*, the results were often negative, but here again some brilliant cures occurred. In the staphylococcal and streptococcal infections the results were more uniformly successful and the same was true with the metastatic complications of gonorrhea. In simple gonorrhea of the urethra the assistance of antiseptic injections has been necessary to effect a cure in most cases.

(Concluded)

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